

NATIONAL PHARMACEUTICAL CONTROL BUREAU
MINISTRY OF HEALTH, MALAYSIA

DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)

First Edition – Revised November 2013

Address:

Lot 36, Jalan Universiti, 46200 Petaling Jaya, Selangor Darul Ehsan, Malaysia



+603-7883 5400



+ 603-7956 2924, 7956 7075



<http://www.bpfk.gov.my>

Please visit the NPCB website for the latest updates



National Pharmaceutical
Control Bureau
Ministry of Health Malaysia



WHO Collaborating Centre
for Regulatory Control of
Pharmaceuticals



Pharmaceutical Inspection
Convention and Pharmaceutical
Inspection Co-operation
Scheme



Certified to ISO 9001:2000
Cert. No: AR 2293



MS ISO/IEC 17025:2005
ISO: 22461:450

GUIDELINE HISTORY

No.	Guideline	Description of Amendment	Effective date
1.	a) Guidelines for Application for Registration of Pharmaceutical Products, Third Edition b) <i>Permohonan Pendaftaran Keluaran Ubat Tradisional</i> , Second Edition	Initial Publication	a) October 1993 b) December 1998
2.	Drug Registration Guidance Document (DRGD)	Merging of 1(a) and 1(b)	* 2004
3.	Drug Registration Guidance Document (DRGD), First Edition - January 2013	Revision of DRGD November 2012	1 st January 2013

*** Note:**

There have been monthly updates of information in the DRGD. The last revision was in November 2012.

This guidance document is [issued by the Director](#) of Pharmaceutical Services under Regulation 29, Control of Drugs and Cosmetics Regulations 1984.

NPCB reserves the right to amend any part of the guidance document whichever it deems fit.

All Rights Reserved.

No part of this guidance document may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, microfilming, recording or otherwise, without written permission from the Senior Director of Pharmaceutical Services, Ministry of Health, Malaysia.

PREAMBLE

- ❖ This “**DRUG REGISTRATION GUIDANCE DOCUMENT (DRGD)**” will serve as the reference guide for the registration process including quality control, inspection & licensing and post-registration activities of medicinal products. This document will replace the “**DRUG REGISTRATION GUIDANCE DOCUMENT**” **Revision of December 2012**.
- ❖ This DRGD shall be read in conjunction with the current laws and regulations together with other relevant legislations, where applicable, governing pharmaceutical and natural products for human use in Malaysia, which include but not limited to the following:
 - a) Sale of Drugs Act 1952;
 - b) Control of Drugs and Cosmetics Regulations 1984;
 - c) Dangerous Drugs Act 1952;
 - d) Poisons Act 1952;
 - e) Medicines (Advertisement & Sale) Act 1956;
 - f) Patents Act 1983;
 - g) Wildlife Conservation Act 2010 (Laws of Malaysia Act 716); and
 - h) International Trade in Endangered Species Act 2008 (Act 686).

The written laws shall take precedence over this guidance document in any event of discrepancy.

- ❖ The scope of this DRGD includes information relating to administrative requirements and procedures for:
 - a) Submission of an application for the registration of medicinal products, which is based on the [ASEAN Common Technical Dossier/ Requirements \(ACTD/ ACTR\)](#), where applicable;
 - b) Submission of an application for the licensing of manufacturers, importers and wholesalers;
 - c) Submission for amendments to a registered medicinal product; and
 - d) Post-registration activities.

- Applicants shall familiarize with the contents of this guidance document and the governing legislations before they submit applications for medicinal product registration.
- The Authority may request for information or specify conditions not described in this document that is deemed necessary to ensure the quality, safety and efficacy of the product.
- An on-going review of regulatory policies will continue, taking into account the global regulatory environment, to allow for timely and pertinent changes.
For more information, please refer to [Circulars](#) and [Newsletters](#).
- Applicants are advised to refer to NPCB's website for the latest updates of the DRGD and other related guidelines. **Separate guidelines** are available for [Cosmetic](#) and [Veterinary products](#).
- The Authority reserves the right to amend any part of the DRGD whenever it deems fit.
- Any enquiry on registration of products may be submitted to:

Secretary,
Drug Control Authority,
National Pharmaceutical Control Bureau,
Ministry of Health Malaysia,
Jalan Universiti, P.O. Box 319,
46730 Petaling Jaya, Selangor.

ABBREVIATIONS AND ACRONYMS

ACCSQ-PPWG	ASEAN Consultative Committee on Standards and Quality/ Pharmaceutical Product Working Group
ACTD	ASEAN Common Technical Dossier
ACTR	ASEAN Common Technical Requirement
AMV	Analytical Method Validation
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient (Interchangeable with drug substance or active substance). The term API Manufacturer is interchangeable with DMF Holder.
ASEAN	Association of Southeast Asian Nations
ATC	Anatomical Therapeutic Chemical
BA	Bioavailability
BE	Bioequivalence
BET	Bacterial Endotoxins Test
BMF	Batch Manufacturing Formula
BP	British Pharmacopoeia
BSE	Bovine Spongiform Encephalopathy
CCL	Centre for Compliance and Licensing
CDCR	Control of Drugs & Cosmetics Regulations 1984
CEO	Chief Executive Officer

CEP	Certificate of Suitability (For Guideline on Registration of API, CEP is referring to Certificate of Suitability of European Pharmacopoeia monographs issued by the EDQM)
CFC	Chlorofluorocarbons
CFS	Certificate of Free Sales
CI	Confidence Interval
CMC	Chemistry, Manufacturing And Controls
CoA	Certificate of Analysis
COH	Change of Product Registration Holder (Previously known as Change of Marketing Authorization Holder)
COMBO	Combination Pack
COS	Change of Manufacturing Site
CPP	Certificate of Pharmaceutical Product
CTX	Clinical Trial Exemption
CTIL	Clinical Trial Import Licence
DCA	Drug Control Authority
DE	Data Exclusivity
DMF	Drug Master File (interchangeable with Active Substance Master File)
DNA	Deoxyribonucleic acid
DRGD	Drug Registration Guidance Document
EDQM	European Directorate for the Quality of Medicine and Healthcare
ELC	Endotoxin Limit Concentration
EMA	European Medicines Agency
EP	European Pharmacopoeia

FDA	Food and Drug Administration
FDI	Food-Drug Interface
FEO	For Export Only
FPQC	Finished Product Specification
FSQD	Food Safety and Quality Division
FTIR	Fourier Transform Infrared
g	gram
GABA	Gamma-Amino Butyric Acid
GC	Gas Chromatography
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GMP	Good Manufacturing Practice
HACCP	Hazard analysis and critical control points
HBsAg	Surface Antigen of the Hepatitis B Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HPLC	High Performance Liquid Chromatography
HS	Health Supplement
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	International Non-proprietary Names

IPQC	In-Process Quality Control
ISO	International Organization for Standardization
JAKIM	Malaysia Department of Islamic Development (<i>Jabatan Kemajuan Islam Malaysia</i>)
JP	Japanese Pharmacopoeia
L	Litre
LAL	Limulus Amebocyte Lysate
LOA	Letter of Authorization
LOC	Letter of Commitment
LOI	Letter of Intent
mAb	monoclonal antibody
max	maximum
MCB	Master Cell bank
MDDCI	Medical Device-Drug-Cosmetic Interface
mL	millilitre
MPN	Most-Probable Number
MSM	Methylsulphonylmethane
MVD	Maximum Valid Dilution
NAT	Nucleic Acid Testing
NCE	New Chemical Entity
NDP	New Drug Product

NMT	Not More Than
NPCB	National Pharmaceutical Control Bureau
NRV	Nutrient Reference Value
OTC	Over-the-Counter
Ph. Eur.	European Pharmacopoeia
PI	Package Insert
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PIL	Patient Information Leaflet
PMF	Plasma Master File
POA	Protocol of Analysis
ppm	parts per million
PRH	Product Registration Holder (Previously known as Marketing Authorization Holder, MAH)
PSUR	Periodic Safety Update Report
PV	Process Validation
RNA	Ribonucleic acid
RSD	Relative Standard Deviation
SIRIM	Standards and Industrial Research Institute of Malaysia
SPC	Summary of Product Characteristics
spp.	Species
Syn.	Synonym

TAMC	Total Aerobic Microbial Count
TGA	Therapeutic Goods Administration
TLC	Thin Layer Chromatography
TSE	Transmissible Spongiform Encephalopathies
TYMC	Total Yeasts and Moulds Count
USP	United State Pharmacopeia
USPI	US Package Insert
UV	Ultra-Violet
VVM	Vaccine Vial Monitor
WCB	Working Cell Bank
WHO	World Health Organisation

GLOSSARY

Indigenous Medicine: As defined under Regulation 2, the CDCR 1984, indigenous medicine means a system of treatment and prevention of disease established through traditional use of naturally occurring substances

Licensed importer: A person to whom an import license has been issued under Regulation 12, CDCR 1984 (*as defined in Regulation 2, CDCR 1984*)

Licensed wholesaler: A person to whom a wholesaler's licence has been issued Regulation 12, CDCR 1984 (*as defined in Regulation 2, CDCR 1984*)

Manufacturer: A company that carries out at least one step of production as well as the final release of the finished product.

Manufacturing: The definition of 'manufacturing' includes:

- a) The making or assembling of the product;
 - b) The enclosing or packing of the product in any container in a form suitable for administration or application, and the labelling of the container and;
 - c) The carrying out of any process in the course of any of the foregoing activities.
- (*as defined in Regulation 2, CDCR 1984*)

Medicinal Product: The term refers to 'product' as stated in Regulation 2, CDCR 1984 which is applicable to pharmaceutical and natural products

OTC: Refers to Generic (Non-Scheduled Poison)

Product Owner: A person, company or entity who is the legal/ registered owner of the product formulation and/or process with whom the marketing authorization holder has a contract (*glossary used in ACTD and ACTR*).

Product Registration Holder: The company or corporate or legal entity in the field of pharmaceuticals whose name the marketing authorization has been granted. This party is responsible to all aspects of the product, including quality and compliance with the conditions of marketing authorization. The authorized holder must be subjected to

legislation in the country that issued the marketing authorization, which normally means being physically located in that country (*glossary used in ACTD and ACTR*).

The Authority: Refers to Drug Control Authority (DCA)

The System: Refers to QUEST system in website of NPCB

Glossary for Homeopathic Products:

Active substance: Active substances are considered to be source materials processed by one or a sequence of homeopathic manufacturing procedures listed in pharmacopoeias in official use and other officially recognized documents (e.g. mother tinctures, dilutions or triturations).

Diluent: Substance used for the preparation of a stock/ starting material or the potentisation process and which may also represent the substance of the dosage form. Liquid diluents usually consist of purified water, aqueous solution, glycerol or ethanol of a suitable concentration or for which there is an appropriate monograph. The commonest solid diluent is usually lactose monohydrate.

Dilution: Dilution has two meanings in homeopathy:

- For a product, a dilution is a liquid homeopathic preparation which is potentised as described below (see the definition of potentisation). Individual dilutions are also called potencies;
- As a procedure, dilution means the de-concentration process of a liquid or a solid preparation. One part of each stage in the preparation of a homeopathic medicine from its stock or previous dilution (potency) by adding one part of a previous solid or liquid phase to a predetermined weight or volume of the diluent (see Potentisation below). Dilution occurs at all stages of production of the homeopathic medicines whether by addition of solid excipient in trituration or the addition of diluent in the liquid phase and succussion.

Dosage form: a dosage form in homeopathy complies with any relevant specifications for that dosage form for which an appropriate characterization exists in a pharmacopoeia in official use, or in other officially recognized documents. The most commonly encountered homeopathic dosage form, *the globule (pillule or pellet)*, is a

solid spherule which consists of lactose, sucrose or any other suitable vehicle. Usually, preformed globules are impregnated with a dilution or directly by a mother tincture. The homeopathic dosage form *tablet* is a solid preparation which complies with any relevant characterization in the pharmacopoeia in official use (or in other officially recognized documents) for tablets. Homeopathic medicines in tablet form are either prepared by impregnation of preformed tablets or by compression of triturations with the vehicle. The most commonly used *liquid homeopathic medicines* are either alcoholic solutions or oral liquids.

Excipient: Substance needed for manufacturing a dosage form (used after potentisation) such as wheat starch and magnesium stearate for tablets. It may also represent the substance of the dosage form.

Homeopath: A qualified provider (practitioner) of homeopathic treatment.

Homeopathic medicines: Any medicine prepared in accordance with a homeopathic manufacturing procedure described by a pharmacopoeia in official use or other officially recognized documents. A homeopathic medicine may contain a number of homeopathic preparations.

Homeopathy: Classical homeopathy is a system of medicine using preparations of substances whose effects, when administered to healthy subjects, correspond to the manifestations of the disorder in the individual patients.

Mother tincture (also called tincture): The initial homeopathic preparation made from source material that can be further potentised (also called “liquid stock”), sometimes used as homeopathic medicines, is regarded as the most concentrated form of a finished homeopathic medicine. Mother tinctures are obtained classically by maceration or percolation (sometimes also by digestion, infusion, decoction or fermentation) techniques from source materials according to a procedure prescribed by a recognized homeopathic pharmacopoeia. Sometimes a mother tincture corresponds to the first decimal dilution, “1D” or “1X” (10-1), mostly when dry plant material is used as starting material.

Nosodes: Homeopathic medicines prepared from disease products from humans or animals; from pathogenic organisms or their metabolic products; or from decomposition products of animal organs.

Potency: The denominated degree of serial trituration or dilution and succession that is reached for each homeopathic medicine. The degrees of dilution or potencies are normally indicated by the letters D, DH or X for successive 1 to 10 (decimal) dilutions, the letters C, CH or K or CK for successive 1 to 100 (centesimal) dilutions while Q or LM denote successive 1 to 50 000 (Hahnemannian quinquagintamillesimal) dilutions. Dilution by 1 to 10 denotes 1 part processed with 9 parts of diluent (Hahnemannian decimal), dilution by 1 to 100, 1 part processed with 99 parts (Hahnemannian or Korsakovian centesimal), and so on. The number preceding the letters (e.g. D, C or LM) normally indicates the number of dilution steps employed (Table 1).

As a consequence of different views in various approaches in homeotherapy and because the notion of these terms may depend on the nature of the starting materials, the terms “high potency” and “low potency” cannot be defined unambiguously.

Potentisation (also called dinamization): The combined process of serial dilution and succussion or trituration at each step in the manufacture of homeopathic medicines from stocks. (According to the tenet of homeopathy, potentisation represents the process by which the activity of a homeopathic medicine is developed.)

Table 1: Potency table

Dilution ratio	Common designation(s)	Examples
1:10 ^a	X	1X, 2X, 3X, etc.
1:10 ^a	D	D1, D2, D3, etc.
1:10 ^a	DH	DH1, DH2, DH3, etc.
1:100 ^b	C	1C, 2C, 3C, etc. C1, C2, C3, etc.
1:100 ^b	CH	1CH, 2CH, 3CH, etc. CH1, CH2, CH3, etc.
1:100 ^b	CK	1CK, 2CK, 3CK, etc. CK1, CK2, CK3, etc.
1:100 ^b	K	1K, 2K, 3K, etc. K1, K2, K3, etc.

1:50 000 ^a	LM	1LM, 2LM, 3LM, etc.
1:50 000 ^a	Q	Q1, Q2, Q3, etc.

^aFor 1:10 and 1:50 000 dilution ratios only the Hahnemannian method of manufacture (multi-flask method) is used.

^bFor 1:100 dilution ratios a C potency is assumed to use the Hahnemannian method of manufacture (multi-flask method) and can also be denoted as CH. When the Korsakovian method of manufacture (single-flask method) is used, the potency is designated as CK or K.

Sarcodes: Homeopathic medicines made from healthy animal tissues or secretions. In Greek, sarcode means fleshly.

Source material (raw material, starting material, mother substance): Source material is the original raw material used for the production of homeopathic medicines. This material is obtained from natural sources, e.g. of botanical, zoological, microbiological, mineral, chemical, animal and human origin, or synthetic procedures. Source materials may undergo preliminary treatment in order to be further processed.

Stock: Substances or preparations made from the source materials (e.g. by maceration, succussion or trituration) used as starting points for the production of homeopathic medicines.

CONTENTS

GUIDELINE HISTORY	2
PREAMBLE	4
ABBREVIATIONS AND ACRONYMS	6
GLOSSARY	12

SECTION A: GENERAL OVERVIEW

1. INTRODUCTION	25
1.1 REGISTRATION OF PRODUCTS	27
1.1.1 REGISTRABLE PRODUCTS	28
1.1.2 NON-REGISTRABLE PRODUCTS	28
1.1.3 EXEMPTIONS FOR PRODUCTS USED IN CLINICAL TRIALS AND MANUFACTURING SAMPLES FOR REGISTRATION	31
1.2 CATEGORIES OF PRODUCT	32
1.2.1 NEW DRUG PRODUCTS	32
1.2.2 BIOLOGICS	34
1.2.3 GENERICS	35
1.2.4 HEALTH SUPPLEMENTS	36
1.2.5 NATURAL PRODUCTS	36
1.3 FOOD - DRUG - INTERFACE PRODUCTS	38
1.3.1 INTRODUCTION	38
1.3.2 CLASSIFICATION OF FDI PRODUCTS	39
1.3.3 PICTORIAL GUIDE TO CLASSIFICATION OF FOOD-DRUG INTERFACE PRODUCTS	42
1.3.4 ADDITIONAL GUIDANCE NOTES FOR FOOD PRODUCTS	44
1.4 MEDICAL DEVICE - DRUG - COSMETIC INTERFACE PRODUCTS	46
1.4.1 INTRODUCTION	46

1.4.2	CLASSIFICATION CRITERIA	46
2.	DATA EXCLUSIVITY	51
2.1	HOW TO APPLY.....	51
2.2	APPLICABILITY AND DATE OF COMING INTO FORCE	52
2.3	GRANT OF DATA EXCLUSIVITY.....	52
2.4	CONSIDERATION OF OTHER APPLICATIONS UPON THE GRANT OF DATA EXCLUSIVITY	54
2.5	NON-APPLICATION OF DATA EXCLUSIVITY	54
2.6	APPEAL.....	55
3.	APPLICATION FORMALITIES	56
3.1	WHO CAN APPLY FOR PRODUCT REGISTRATION	56
3.2	RESPONSIBILITY OF APPLICANT.....	56
3.3	HOW TO APPLY.....	57
4.	FEES	58
4.1	FEES IMPOSED.....	58
4.2	MODE OF PAYMENT.....	58
5.	TYPES OF APPLICATION.....	59
5.1	REGISTRATION OF PRODUCTS	59
5.1.1	APPLICATION FOR PRODUCT REGISTRATION FOR THE FOLLOWING CATEGORIES:	59
5.1.2	REGISTRATION OF COMBINATION PACK (COMBO PACK)	59
5.1.3	REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)	61
5.2	AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT	61
5.2.1	VARIATION	61
5.2.2	CHANGE IN MANUFACTURING SITE	62
5.2.3	CHANGE IN PRODUCT REGISTRATION HOLDER	62
5.2.4	NEW/ ADDITIONAL INDICATION	62
5.2.5	APPLICATION FOR A CONVENIENT PACK.....	63
5.3	RENEWAL OF PRODUCT REGISTRATION.....	63

5.4	CERTIFICATES.....	63
5.4.1	CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP).....	63
5.4.2	GOOD MANUFACTURING PRACTICE (GMP) CERTIFICATE	64
5.5	LICENSES.....	64
5.6	CLINICAL TRIAL IMPORT LICENCE (CTIL)/ CLINICAL TRIAL EXEMPTION (CTX)	65
6.	GENERAL CONDITIONS FOR REGISTRATION OF DRUG PRODUCTS UNDER THE CONTROL OF DRUGS AND COSMETICS REGULATIONS 1984	66
6.1	REGISTRATION NUMBER	66
6.2	PRODUCT PARTICULAR	66
6.3	LABELLING	67
6.4	PRODUCT AUTHENTICATION.....	67
6.5	INDICATIONS, SPECIAL CONDITIONS	68
6.6	ADVERSE REACTIONS, COMPLAINTS.....	68
6.7	HOLDER OF REGISTRATION CERTIFICATE.....	68
6.8	WITHDRAWAL FROM REGISTRATION	68
6.9	CANCELLATION, SUSPENSION, AMENDMENT BY THE AUTHORITY	68
6.10	DIRECTIVES	69
7.	USE OF <i>HALAL</i> LOGO.....	70

SECTION B: PRODUCT REGISTRATION PROCESS

8.	FLOW OF REGISTRATION PROCESS.....	71
8.1	PRE-SUBMISSION OF APPLICATION	72
8.1.1	CATEGORY OF PRODUCT	72
8.1.2	METHOD OF EVALUATION	72
8.1.3	REQUIREMENTS FOR PRODUCT REGISTRATION.....	75
8.1.4	CONDITIONS APPLIED ON PRODUCT REGISTRATION	76

8.1.5	MULTIPLE APPLICATIONS	77
8.1.6	SECOND OR THIRD SOURCE	77
8.1.7	VARIANTS	78
8.1.8	LANGUAGE	79
8.2	SUBMISSION OF APPLICATION	79
8.3	SCREENING OF APPLICATION	80
8.3.1	SATISFACTORY	80
8.3.2	NON-SATISFACTORY	81
8.4	EVALUATION OF APPLICATION	82
8.4.1	INITIATION OF REVIEW	82
8.4.2	CORRESPONDENCE	82
8.4.3	STOP CLOCK	82
8.4.4	TIMELINE FOR PRODUCT REGISTRATION	83
8.5	REGULATORY OUTCOME	84
8.5.1	DECISIONS OF THE AUTHORITY	84
8.5.2	PRODUCT REGISTRATION NUMBER	84
8.5.3	CERTIFICATE OF REGISTRATION	84
8.6	POST-REGISTRATION PROCESS	85
8.7	REJECTED APPLICATION	85
8.7.1	PROCESS OF APPEAL FOR QUEST 2 PRODUCT	86
8.7.2	PROCESS OF APPEAL FOR QUEST 3 PRODUCT	87
8.7.3	TEMPLATE FOR AN APPEAL LETTER	88

SECTION C: QUALITY CONTROL

9.	GUIDELINE FOR THE SUBMISSION OF PROTOCOL OF ANALYSIS (POA)	90
9.1	GENERAL REQUIREMENTS	90
9.2	SPECIFIC REQUIREMENTS	91

10. GUIDELINE FOR THE SUBMISSION OF ANALYTICAL METHOD VALIDATION	
(AMV) DOCUMENTS	96
10.1 TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED	96
10.2 TYPICAL VALIDATION PARAMETERS FOR CHEMICAL TESTS	96
10.2.1 FULL VALIDATION FOR IN-HOUSE METHODS.....	96
10.2.2 PARTIAL VALIDATION FOR COMPENDIAL/ PHARMACOPOEIAL	
METHODS.....	98
10.3 TYPICAL VALIDATION CHARACTERISTICS FOR MICROBIOLOGICAL	
TESTS:	99
11. GUIDELINE FOR THE SUBMISSION OF PRODUCT SAMPLES FOR	
LABORATORY TESTING	100
11.1 GENERAL REQUIREMENTS	100
11.2 SPECIFIC REQUIREMENTS	101
11.2.1 NATURAL PRODUCTS	101
11.2.2 PHARMACEUTICAL PRODUCTS	101
11.3 APPEAL FOR RETESTING	102

SECTION D: INSPECTION AND LICENSING

12. INSPECTION.....	103
12.1 FOREIGN GMP INSPECTION	104
13. LICENSING	104
13.1 TYPES OF LICENSES	105
13.2 LICENSE APPLICATION FORM	105
13.3 ADDITIONAL LIST OF LICENSE FOR REGISTERED PRODUCTS.....	106
13.4 GMP CERTIFICATE	106

SECTION E: POST-REGISTRATION PROCESS

14.	MAINTENANCE OF REGISTRATION	107
15.	WITHDRAWAL OF PRODUCT REGISTRATION	107
16.	AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT	108
16.1	VARIATION	108
16.1.1	VARIATION APPLICATION FOR FULL EVALUATION PRODUCTS	108
16.1.2	VARIATION APPLICATION FOR ABRIDGED EVALUATION PRODUCTS ...	110
16.1.3	OTHER INFORMATION.....	113
16.2	CHANGE OF MANUFACTURING SITE	114
16.2.1	CONDITIONS ON APPLICATION FOR COS:	114
16.2.2	CONDITIONS ON GOOD MANUFACTURING PRACTICE (GMP):	114
16.2.3	TYPES OF MANUFACTURING SITE CHANGES (COS)	115
16.2.4	MODE OF SUBMISSION	117
16.2.5	OTHER INFORMATION.....	117
16.3	CHANGE OF PRODUCT REGISTRATION HOLDER	118
16.3.1	INTRODUCTION	118
16.3.2	CONDITIONS	118
16.3.3	APPLICATION.....	119
16.3.4	PROCESSING FEE.....	119
16.3.5	SUPPORTING DOCUMENTS.....	120
16.3.6	SUPPORTING DOCUMENT FORMAT EXAMPLE	121
16.3.7	FLOWCHART FOR THE CHANGE OF PRODUCT REGISTRATION HOLDER	123
16.4	NEW/ ADDITIONAL INDICATION	124
16.4.1	FULL EVALUATION PROCESS.....	124
16.4.2	VERIFICATION PROCESS	124
16.5	APPLICATION FOR A CONVENIENT PACK	125
17.	POST-MARKETING ACTIVITIES.....	127

17.1 PHARMACOVIGILANCE	127
17.1.1 ADVERSE DRUG REACTION REPORTING AND SAFETY UPDATES	127
17.2 POST-MARKET SURVEILLANCE	128
17.2.1 PRODUCT COMPLAINTS.....	128
17.2.2 PRODUCT RECALLS.....	129
17.3 PUNITIVE ACTION FROM THE AUTHORITY	129
17.3.1 ADULTERATION.....	129
APPENDICES.....	130
APPENDIX 1: FEES.....	131
APPENDIX 2: REQUIREMENTS FOR PRODUCT REGISTRATION	136
APPENDIX 3: GUIDELINES ON REGISTRATION OF BIOLOGICS.....	155
APPENDIX 4: GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS	178
APPENDIX 5: GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS	240
APPENDIX 6: GUIDELINE ON REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS (API).....	313
APPENDIX 7: SPECIAL CONDITIONS FOR REGISTRATION FOR A PARTICULAR PRODUCT OR GROUP OF PRODUCTS	330
APPENDIX 8: LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES	333
APPENDIX 9: LABELLING REQUIREMENTS.....	347
APPENDIX 10: GUIDELINE ON PATIENT DISPENSING PACK FOR PHARMACEUTICAL PRODUCTS IN MALAYSIA	430
APPENDIX 11: GUIDELINE ON FILLING THE ONLINE APPLICATION FORM FOR PRODUCT REGISTRATION VIA QUEST SYSTEM	439
APPENDIX 12: CONDITIONS AND SUPPORTING DOCUMENTS REQUIRED FOR AN APPLICATION OF VARIATION.....	460

APPENDIX 13: SUPPORTING DOCUMENTS REQUIRED FOR CHANGE OF MANUFACTURING SITE (COS) APPLICATION.....	484
LIST OF UPDATES	487

SECTION A: GENERAL OVERVIEW

1. INTRODUCTION

The [Control of Drugs and Cosmetics Regulations \(CDCR\) 1984](#) were promulgated under the [Sale of Drugs Act 1952](#). The Authority (known as Drug Control Authority, DCA) established under these Regulations, is tasked with ensuring the quality, safety and efficacy of medicinal products through the registration, including quality control, inspection & licensing and post-registration activities. The National Pharmaceutical Control Bureau (NPCB) acts as the secretariat to the Authority.

Under the CDCR 1984, Regulation 7(1): Except as otherwise provided in these Regulations, no person shall manufacture, sell, supply, import, possess or administer any product unless:

- (a) the product is a registered product; and
- (b) the person holds the appropriate licence required and issued under these Regulations.

The phases of implementation for product registration are as shown in **Figure 1** below:

Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
Registration Aug 1985 (Prescription Drugs)	Registration 1988 (OTC)	Registration Jan 1992 (Traditional Medicine)	Registration Feb 2002 (Cosmetics)	Registration Aug 2007 (Veterinary)	Regulatory control of Active Pharmaceutic al Ingredient (API)**
Licensing May 1987	Licensing 1992	Licensing Manufacturer Importers Jan 1999	Licensing Jan 2004	Licensing 1 Jan 2012*	No licensing Requirements as registration of API is linked to products

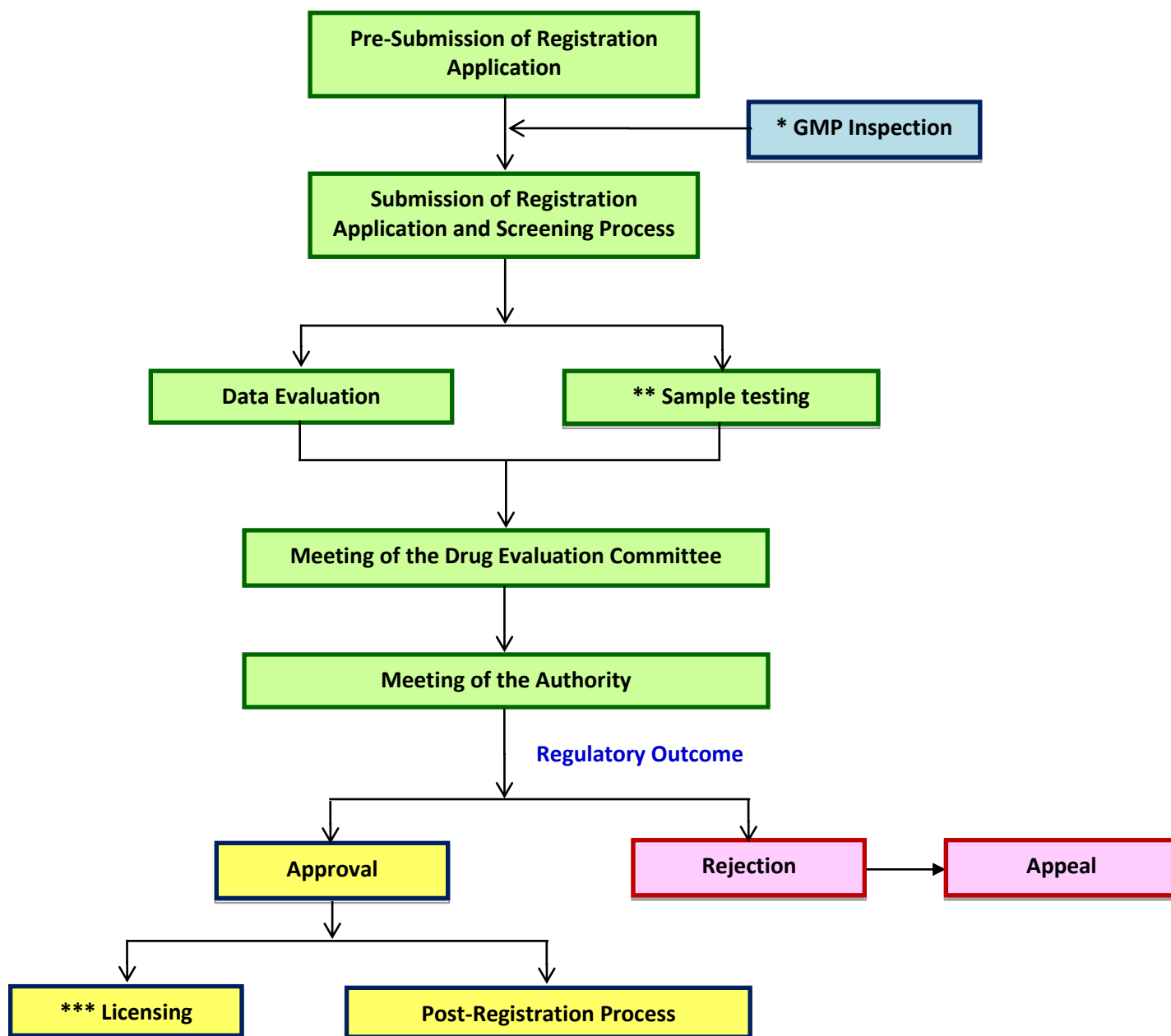
* 1st July 2012:

All manufacturers shall be certified for GMP as directed via Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Tahun 2012*

Reference: Circulars [Bil \(25\) dlm BPFK/PPP/01/03 Jld 1](#) and [Bil \(96\) dlm BPFK/PPP/01/03 Jld. 2](#)

** Voluntary registration of API commenced in April 2011, started with New Drug Products (NDP), followed by mandatory registration of API for NDP which were implemented in January 2012. As for Generics, the mandatory registration of API will be announced at a later date.

Registration process includes quality control, inspection & licensing as well as post-registration process of medicinal products is illustrated in **Figure 2** below:



* Good Manufacturing Practice (GMP) Certification

** For natural products only

*** Application for Manufacturer, Import and/or Wholesale License

1.1 REGISTRATION OF PRODUCTS

Under the CDCR 1984, Regulation 2: “**Product**” means:

- (a) a drug¹ in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose²; or
- (b) a drug¹ to be used as an ingredient of a preparation for a medicinal purpose².

Under Sales of Drug Act 1952, Section 2:

¹ “**drug**” includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for a medicinal purpose.

² “**medicinal purpose**” means any of the following purposes:

- (a) alleviating, treating , curing or preventing a disease or a pathological condition or symptoms of a disease;
- (b) diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;
- (c) contraception;
- (d) inducing anaesthesia;
- (e) maintaining, modifying, preventing, restoring, or interfering with, the normal operation of a physiological function;
- (f) controlling body weight;
- (g) general maintenance or promotion of health or wellbeing.

Note:

In this DRGD, the term “medicinal product” refers to the term “product” as stipulated in the Regulation 2, CDCR 1984.

1.1.1 REGISTRABLE PRODUCTS

Any product as defined in 1.1 shall be registered with the Authority.

The products include, but not limited to the following:

- a) Pharmaceutical products containing scheduled poisons
- b) Pharmaceutical products containing non-scheduled poisons
(For examples: Medicated plaster with medicine, antiseptic/ disinfectants for use on the human body, diagnostic agents for human use (in-vivo) and health supplement such as probiotics and chitosan)
- c) Natural products
Includes herbal and traditional products

1.1.2 NON-REGISTRABLE PRODUCTS

- i) Diagnostic agents and test kits for laboratory/ in-vitro use

Diagnostic agents/ test kits for laboratory use must be labeled '**FOR LABORATORY USE ONLY**'.

Note:

Products which are not labelled as such shall be deemed to be for human or animal use and need to be registered with the Authority.

- ii) Medical Devices

“Medical device” means any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article intended by the manufacturer to be used, alone or in combination, for human beings for the purpose of:

- (i) diagnosis, prevention, monitoring, treatment or alleviation of disease;
- (ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury;
- (iii) investigation, replacement or modification, or support of the anatomy or of a physiological process;
- (iv) support or sustaining life;
- (v) control of conception;
- (vi) disinfection of medical device; or
- (vii) providing information for medical or diagnostic purpose by means of *in vitro* examination of specimens derived from the human body,

These products do not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its intended function by such means.

This includes but is not limited to the following:

- Non-medicated bandages, plaster
- Surgical dressings, wound care/ dressing materials containing hydrogel, collagen, calcium alginate
- Visco-elastic products for mechanical or physical protection of tissues during or after surgical procedures
- Instruments, apparatus, syringes, needles, sutures, catheters
- Disinfectants for equipments/ devices
- Lubricants for gloves, condoms and endoscopes
- Contact lens care products
- Copper IUDs
- Bone cement, tissue adhesives
- Dental fillings
- Blood bags containing anti-coagulants
- Non-medicated medical and contraceptive devices

For more information, please refer [Medical Device Bureau](#).

iii) Food

As defined under the Food Act 1983 and Food Regulations 1985, includes every article manufactured, sold or represented for use as food or drink for human consumption or which enters into or is used in the composition, preparation, and preservation, of any food or drink and includes confectionery, chewing substances and any ingredient of such food, drink, confectionery or chewing substances. This includes food for special dietary use for persons with a specific disease, disorder or medical condition, and food which contain quantities of added nutrients allowable under the Food Act 1983 and Regulations.

For more information, please refer [Food Safety & Quality Division, Ministry of Health Malaysia](#).

iv) Sports Nutrition, such as body-building products containing protein/ whey/ soya bean

v) Raw herbs used in extemporaneous preparations, including those that are dried & cut into pieces, without dosage instructions and indications

vi) Insect repellants, insecticides, pesticides and parasitocides

Products containing pesticides as listed under First Schedule of Pesticide Act 1974 for external use only shall be controlled by the Pesticide Board.

For more information, please refer <http://www.doa.gov.my>

vii) Detergents/ disinfectants for domestic use

1.1.3 EXEMPTIONS FOR PRODUCTS USED IN CLINICAL TRIALS AND MANUFACTURING SAMPLES FOR REGISTRATION

a) Clinical Trial Import License (CTIL)

Products which are not registered with the Authority and are intended to be imported for the purpose of clinical trial shall have a Clinical Trial Import License.

This is in accordance to the Regulation 12(1)(c), CDCR 1984: “The Director of Pharmaceutical Services may, subject to the provisions of these Regulations, issue the following license subject to such conditions as he may impose, a clinical trial import license in Form 4 in the Schedule, authorizing the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product”.

b) Clinical Trial Exemption (CTX) & Exemption for Manufacturing Sample for Registration

- i) Products which are not registered with the Authority and are intended to be manufactured locally for the **purpose of clinical trial** shall require Clinical Trial Exemption (CTX) from the Director of Pharmaceutical Services; and
- ii) Any person who wishes to manufacture any product solely for the **purpose of producing a sample for registration** should apply for an exemption for manufacture of sample. (Applies to **locally manufactured products only**).

This is in accordance to the Regulation 15(5), CDCR 1984: “Any person who wishes to manufacture any product solely for the purpose of producing samples for clinical trials, for registration or issuance of notification note under these Regulation may on application be exempted by the Director of Pharmaceutical Services from the provisions of regulation 7 (1) or regulation 18A”.

For more information, please refer Regulation 15, CDCR 1984: Exemptions & Saving; and [Guidelines on Clinical Trial](#).

1.2 CATEGORIES OF PRODUCT

Note:

Before submission of application for a product registration, applicants may verify via [Classification Form](#) if unsure for the product category.

Medicinal products for registration are classified under the following categories:

1.2.1 NEW DRUG PRODUCTS

New Drug Products (NDP) is defined as any pharmaceutical products that have not been previously registered in accordance with the provisions of the CDCR 1984.

An NDP may be classified according to the following categories:

a) New Chemical Entity (NCE)/ Radiopharmaceutical Substance

A new pharmaceutical product containing any of the following:

i. New Chemical Entity (NCE)

Defined as an active moiety that has not been registered in any pharmaceutical product.

ii. Radiopharmaceutical substance

Defined as a radionucleotide, ligand or the coupling mechanism to link the molecule and the radionucleotide that has not been registered in any pharmaceutical product.

b) New Combination Product

A new pharmaceutical product containing two or more drugs that are physically, chemically or otherwise combined or mixed and produced

as a single pharmaceutical product, in a combination that has not been registered in any other pharmaceutical product. This includes any of the following:

- i. Combination of New Chemical Entities;
- ii. Combination of registered chemical entity(s) AND New Chemical Entity(s);
- iii. Combination of registered chemical entities;
- iv. Combination of registered chemical entities in a new chemical forms;
- v. Combination of registered chemical entity(s) in new chemical form(s) AND New Chemical Entity(s);
- vi. Combination of registered chemical entity(s) in new chemical form(s) AND registered chemical entity(s).

c) Supplemental Product

A new pharmaceutical product containing a drug that has been previously registered as a pharmaceutical product but differing in properties with regards to safety and/or efficacy from the product that has been previously registered.

This includes any of the following:

- i. Registered chemical entity in a new chemical form;
- ii. Registered chemical entity in a new dosage form;
- iii. Registered chemical entity in a new dosage strength with a change in dosing/ posology;
- iv. Registered chemical entity for use by a new route of administration;
- v. Registered chemical entity for new indication(s), dosage recommendation(s) and/or patient population(s).

1.2.2 BIOLOGICS

- The term 'biopharmaceutical' was coined in the 80's to define proteins that were made by recombinant DNA technology [which includes hybridoma technology for monoclonal antibody (mAb) production].
- Biologic/ Biological product refers to a product whose active substance is made by or derived from a living organism (plant, human, animal or microorganism) and may be produced by biotechnology methods and other cutting-edge technologies. This product imitates natural biological substances in our bodies such as hormones, enzymes or antibodies.
- Biological substance is defined as a substance that is produced by or extracted from a biological source and that needs, for its characterization and the determination of its **quality**, a combination of physicochemical-biological testing together with the production process and its controls.
- Biopharmaceuticals/ Biologics/ Biological products can also be defined as: "a protein (including antibodies) or nucleic acid-based pharmaceuticals used for therapeutic, which is produced by means other than direct extraction from a native (non-engineered) biological source". This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant/ genetically engineered and mAb-based products).
- The term 'Biotechnology product' and 'Biological product' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view).

Note:

Today, biologics have become inextricably intertwined with biopharmaceuticals, to the point where they are synonymous. The general consensus is that the term 'Biologic' and 'Biopharmaceutical' are interchangeable.

Biologics include a wide range of products such as:

- Vaccines;
- Blood products;
- Monoclonal antibodies (therapeutics);

- Recombinant proteins:
 - Insulins
 - Hormones
 - Erythropoietins and other hematopoietic factors
 - Cytokines: Interferons, interleukins, colony-stimulating factors, tumour necrosis factors.

But does not include:

- Metabolites from microorganisms; e.g. antibiotics and some hormones;
- Macromolecules produced by chemical synthesis; e.g. peptides/ oligo-nucleotides produced by chemical synthesis;
- Whole blood or cellular blood components.

Note:

This document is not intended to apply on the control of genetically modified live organisms designed to be used directly in humans, e.g. live vaccines

For details, please refer [Appendix 3: Guideline on Registration of Biologics](#) and [Guideline on Registration of Biosimilars in Malaysia](#)

1.2.3 GENERICS

A generic product is a product that is essentially similar to a currently registered product in Malaysia. However, the term generic is not applicable to Biologics.

Generics may be further classified into two groups:

1. Scheduled Poison

(Known as Controlled Medicine/ Controlled Poison)

Products containing poisons as listed in the First Schedule under [Poisons Act 1952](#).

2. **Non-scheduled Poison**

(Known as Non-Poison or “Over-the-Counter”, OTC)

Products containing active ingredients which are not listed in the First Schedule under Poisons Act 1952; and is excluding active ingredient which is categorized under health supplements or natural products or cosmetics.

1.2.4 HEALTH SUPPLEMENTS

A Health Supplement (HS) means any product that is used to supplement a diet and to maintain, enhance and improve the health function of human body. It is presented in small unit dosage forms (to be administered) such as capsules, tablets, powder, liquids and shall not include any sterile preparations (i.e. injectables, eyedrops). It may contain one or more, or the following combination:

- i) Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics, and other bioactive substances;
- ii) Substances derived from *natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolite;
- iii) Synthetic sources of ingredients mentioned in (i) and (ii) may only be used where the safety of these has been proven.

For details, please refer to [Appendix 4](#): Guidelines for Registration of Health Supplements

1.2.5 NATURAL PRODUCTS

a) Traditional medicine (as defined under the Control of Drugs and Cosmetics Regulations 1984):

Any product used in the practice of indigenous medicine, in which the drug consist solely of one or more naturally occurring substances of a plant, animal

or mineral, of parts thereof, in the unextracted or crude extract form, and a homeopathic medicine. It shall not include any sterile preparation, vaccines, any substance derived human parts, any isolated and characterized chemical substances.

b) Finished Herbal Product

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term “mixture herbal product” can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substance have been added, including synthetic compounds and/ isolated constituents from herbal materials, are not considered to be herbal.

c) Herbal Remedy

Any drug consisting of a substance or a mixture of substances produced by drying, crushing or comminuting, but without subjecting to any other process, a natural substance or substances of plant, animal or mineral origin, or any part of such substance or substances.

d) Homeopathic Medicine

Any pharmaceutical dosage form used in the homeopathic therapeutic system in which diseases are treated by the use of minute amounts as of such substances which are capable of producing in healthy persons symptoms similar to those of the disease being treated.

For details, please refer to [Appendix 5: Guidelines for Registration of Natural Products](#)

1.3 FOOD - DRUG - INTERFACE PRODUCTS

This guide serves to assist in determining if a product is to be regulated by the National Pharmaceutical Control Bureau (NPCB) or the Food Safety and Quality Division (FSQD) of the Ministry of Health Malaysia.

1.3.1 INTRODUCTION

Malaysians are now more health conscious and there is generally greater awareness of the importance of the nutrition to overall well-being. In recent years, many consumers also rely on a variety of “dietary supplements” to improve their health. These diverse products are freely available through a myriad of outlets. A variety of products are available in the market, supposedly for the maintenance, prevention and even treatment of chronic diseases. These products may range from foods modified to have special properties or pure forms of vitamins and minerals to extract of various botanical or animal products.

It is important to monitor and regulate the marketing and sale of these products so as to protect the interest of the consumer. Some of these products are not clearly marketed as “food” or “drugs”. These have been termed as “food-drug interface (FDI) products” and include a variety of so-called health products.

Previously, it had been difficult to determine which authority within the Ministry of Health Malaysia should regulate the marketing and sale of such products, either FSQD or NPCB. This has caused difficulty to the companies intending to market such products. It is also not beneficial to the consumer as the products could be in the market and not regulated by either of the authorities.

To overcome these problems and to enable a decision to be made as to which authority should regulate a particular product, the Committee for the Classification of Food-Drug Interface Products has been formed since year 2000. The main terms of reference of the Committee is to assist the FSQD and NPCB in classifying, in a consistent manner, an application from the industry which is not clearly defined as a food or drug product that is a FDI product. Other duties include advising the two divisions of the Ministry of Health in strengthening and updating the relevant regulations as well as to provide scientific input on these products.

1.3.2 CLASSIFICATION OF FDI PRODUCTS

The Committee for the Classification of Food-Drug Interface Products, comprising of members from FSQD and NPCB has established a system for the classification of FDI products.

This classification is based on multiple criteria, as outlined below:

a) Main criteria

The ingredients of the product are the main criteria of this classification process:

- i) If the product content close to 100% of active ingredients, e.g. amino acids & peptides, collagen, coral calcium, dietary fibre, enzymes, fatty acids, live microorganism, minerals, plant stanol/ sterol & esters, vitamins, etc, the product has to be regulated by NPCB.
- ii) Substances or ingredients used for therapeutic purposes shall not be added to food. For examples: gypsum fibrosum, pearl powder and [gamat \(stichopus spp.\)](#), [Glutathione](#), [Hyaluronic Acid](#), [Red Yeast Rice](#), [Natto Extract](#), [Placenta](#), [Bile](#), [GABA](#), [Resveratrol And Glucosamine](#).
- iii) # A product content close to 100% of a herb or a mixture of herbs that are not traditionally used as food and possess medicinal values if shall be regulated by NPCB. Examples of such products are aloe vera, alfafa, barleygrass, dukung anak, gamat extract, kacip fatimah, manjakani, mas cotek, misai kucing, noni extract, royal jelly, spirulina, tongkat ali, tunjuk langit, wheatgrass, psyllium husk, pegaga tablet, and rooibos tea.
- iv) # Herbs and spices that are traditionally used in food preparation shall be regulated by FSQD e.g. black cumin (habbatus sauda), garlic, ginger, pegaga, traditional chinese raw herbs, turmeric.
- v) Products containing a mixture of food ingredients with active ingredients and/or herbs identified in point marked with # above shall be classified according to the 80:20 ratio general rule below, unless otherwise specified.

- If a product contains more than 20% of the active ingredients or natural ingredients with pharmacological and/or therapeutic properties, such a product shall be regulated by NPCB.
 - If a product contains equal to or less than 20% of active ingredients or natural ingredients with pharmacological and/or therapeutic properties, the product shall be regulated by FSQD.
 - Notwithstanding this general rule, if a product contains specific active ingredients which possess high pharmacological or therapeutic potencies, the product may be regulated by NPCB even if these active ingredients are present in less than 20%.
- vi) When there is greater uncertainty regarding the safety of a product, it shall be regulated by NPCB. This is to enable closer monitoring of such products, so as to safeguard the interest of the consumer.
- vii) Notwithstanding the above points, the following ingredients do not follow the 80:20 ratio general rule mentioned above and shall be regulated by NPCB:
- Plant sterols/ stanols and esters that are consumed $\geq 3.5\text{g/day}$
 - Psyllium husk that are consumed $\geq 3.5\text{g/day}$

b) Other criteria

The following may be used as additional criteria to assist in the classification of FDI products:

i) Intended use and claims made by the product

Eventually, if a product has been decided to be regulated by FSQD, no claims should be made, other than those permitted by the Food Regulations.

ii) Dosage form

- Any foods or combination of foods that are regulated under FSQD shall not be in the form of soft gel, capsule or tablet that is to be directly swallowed.

- Any product to be regulated under NPCB shall not be in the conventional food form such as cake, muffins, biscuits, gummy, jelly, chocolate, premix beverages etc.

iii) Unusual application

- Products with unusual application for example spray may not be accepted by FSQD.
- Products of coffee/ tea (coffea species/ camellia sinensis) containing herbs and a mixture of creamer and sugar are **not allowed** to be registered under category of natural product by NPCB.

iv) Oils in pharmaceutical dosage form

Oils that are not traditionally used as food or are in combination with edible oil for example evening primrose oil, garlic oil, fish oil, flaxseed oil and grapeseed oil in capsule or soft gel shall be regulated by NPCB.

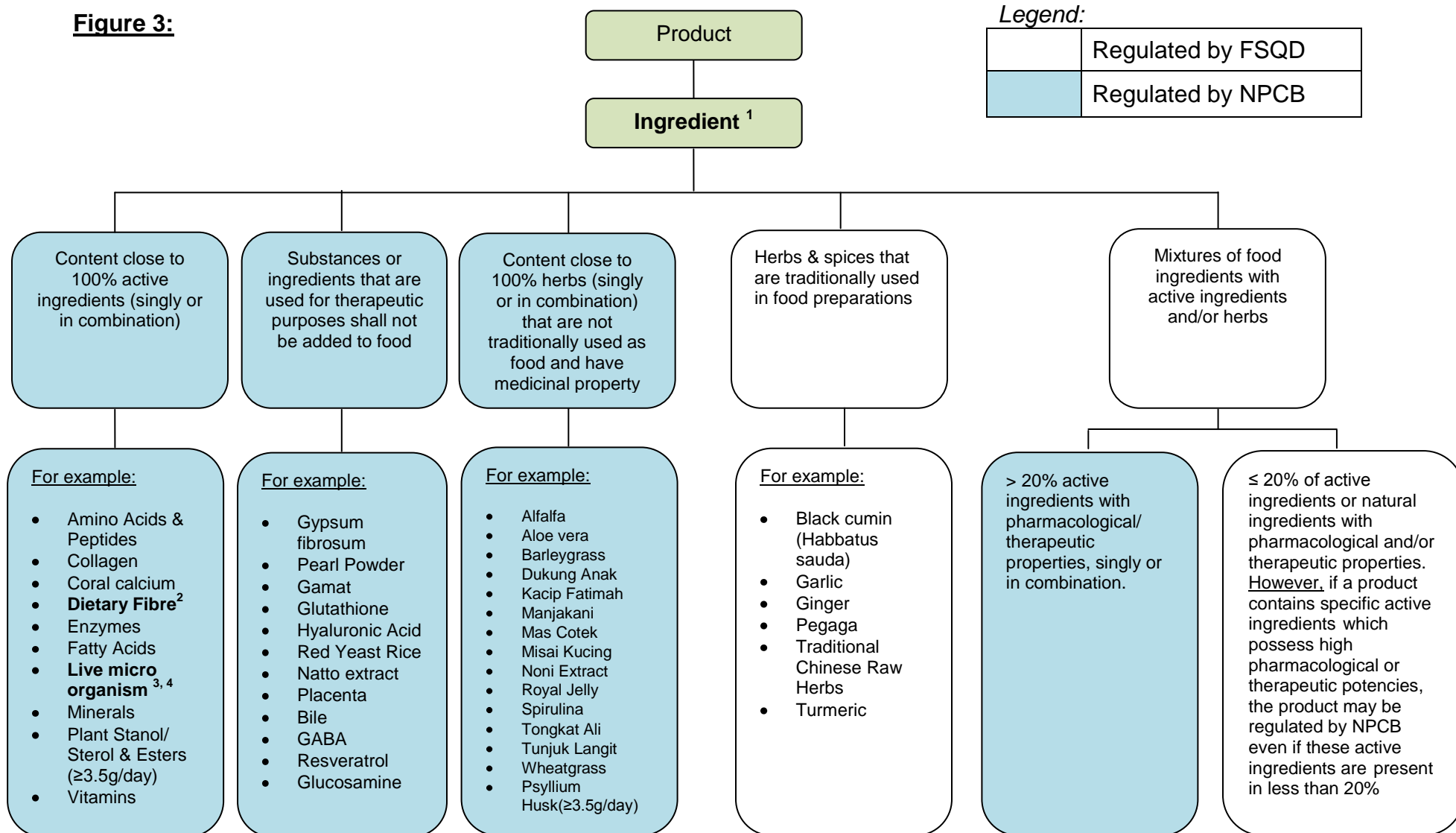
Notes:

Applicant shall verify on FDI product classification with NPCB in order to determine whether the product shall be registered by the Authority or otherwise.

Reference: [Circular \(97\)d/m.BPFK/PPP/01/03 Jld. 2](#)

1.3.3 PICTORIAL GUIDE TO CLASSIFICATION OF FOOD-DRUG INTERFACE PRODUCTS

Figure 3:



Notes:

- ¹ Substances listed in the prohibited ingredient list of the Drug Registration Guidance Document (DRGD) and Schedule Poison shall not be permitted for use in any product.
- ² Dietary fibre includes inulin, fructooligosacharrides, galactooligosacharrides, polydextrose, acacia gum, oat soluble fibre, resistant dextrose and resistant maltodextrine.
- ³ Permitted live microorganism when present by itself singly or in combination in pharmaceutical dosage form shall be regulated under NPCB and shall contain minimum of 10^6 cell/g of the viable cells for each strain.
- ⁴ Permitted live microorganism when present in foods shall be treated as food ingredient and shall contain minimum of 10^6 viable cells/g of the viable cells, depending on the strains.

1.3.4 ADDITIONAL GUIDANCE NOTES FOR FOOD PRODUCTS

a) Foods

Under Section 2, Food Act 1983:

"Food" includes every article manufactured, sold or represented for use as food or drink for human consumption or which enters into or is used in the composition, preparation, preservation, of any food or drink and includes confectionery, chewing substances and any ingredient of such food, drink, confectionery or chewing substances.

All food products must comply with the Food Act 1983 and Food Regulations 1985.

b) List of Food Products that may contain Herbs or Botanical Plants under Food Regulations 1985

- Meat extract or meat essence
- Botanical Beverage Mix (regulation 356)
- Mixed Food Products
- Food standards that contain words: "may contain other food"

c) Permitted Added Nutrients in Food Products

For details, please refer to Food Regulations 1985, Table 1 under the Twelfth Schedule.

d) Maximum Amounts of Vitamins and Minerals permitted in Food, as shown in **Table I** below:

Added Nutrient	Maximum amount in recommended daily serving
Vitamin A	5,000 I.U.
Thiamine	2.2 milligram
Riboflavin	3.2 milligram
Pyridoxine	4 milligrams

Added Nutrient	Maximum amount in recommended daily serving
Biotin	400 micrograms
Pantothenic acid	14 milligrams
Niacin	22 milligrams
Ascorbic acid	100 milligrams
Vitamin D	800 I.U.
Vitamin E	50 I.U.
Calcium	1.4 grams
Iodine	200 micrograms
Iron	20 milligrams
Phosphorus	1.4 grams
Folic acid	400 micrograms
Vitamin B ₁₂	4 micrograms

e) Permitted Bifido Bacteria in Food, as shown in **Table II** below:

PERMITTED BIFIDO BACTERIA IN FOOD

Name	Minimum viable cells/g
Bifido bacterium lactis (L-form)	10 ⁶
Bifido bacterium longum (L-form)	10 ⁶

1.4 MEDICAL DEVICE - DRUG - COSMETIC INTERFACE PRODUCTS

1.4.1 INTRODUCTION

The Committee for the Classification of Medical Device-Drug-Cosmetic Interface (MDDCI) Products, comprising of members from Medical Device Authority and NPCB, has established a system for the classification of MDDCI products.

Registration of drug products/ notification of cosmetics that has been classified must follow the requirements that have been set forth as follows:

- a) **Drugs & Cosmetics** – The registration/ notification regulated by the NPCB is in accordance with the requirements set forth in the Poisons Act 1952 and its Regulations, Sales of Drugs Act 1952 and the Control of Drugs and Cosmetics Regulations 1984;
- b) **Medical Device** – The registration regulated by Medical Device Authority is in accordance with the requirements set forth in the Medical Devices Act 2012 (Act 737).

For **Drug-Device Combination Product**, it will be regulated according to the classification that has been made and by the relevant agencies.

1.4.2 CLASSIFICATION CRITERIA

The following may be used as criteria to assist in the classification of products:

- a) The primary intended purpose of the product;
- b) The primary mode of action/ the principal mechanism of action by which the claimed effect or purpose of the product is achieved;
 - i) Medical device is based on function by physical means, e.g. mechanical action, creation of a physical barrier or replacement or support of organ or body function;
 - ii) Drug is based on pharmacological, immunological or metabolic action in/on the body.
- c) Active ingredient, indication and pharmaceutical dosage form (these are the main criteria for classification of the drugs);

d) Classification of the products in reference countries.

For classification of MDDCI products as decided by the committee, please refer **Table III** and it shall be used as guidance for classification only.

Table III: Summary of Product Classification Decision

NO.	PRODUCT	INTENDED PURPOSE OR INDICATION	CATEGORY
1	<u>Eye Lubricant</u>	A sterile substance used to provide supplemental lubrication/ hydration to the natural eye to treat dry, tired, and/or strained eyes resulting from dry eye syndrome, ageing/ hormone changes (menopause), or environmental factors (e.g. pollution and air conditioning).	MEDICAL DEVICE
2	<u>Irrigation solutions</u>	For mechanical cleansing and rinsing including those used in the eye such as for cleansing of the eye, body tissues, body cavities, wounds or irrigation of a special tube called a catheter which is used to drain the bladder.	MEDICAL DEVICE (If it contains pharmacologically active substance, it will be classified as DRUG)
3	<u>Medical gases</u>	To be used in anaesthesia and inhalation therapy, including their primary containers.	DRUG
4	<u>Medical gases</u>	For in-vivo diagnostic purposes including lung function tests.	DRUG
5	<u>In vivo diagnostic agents</u>	For diagnostic purposes, carrier solutions to stabilize micro bubbles for ultrasound imaging.	DRUG
6	<u>Hyaluranon based products</u> used as; a) Synthetic-fluid tissue reconstructive material	To correct cutaneous contour deformities of the skin (e.g. wrinkles, folds, scars), particularly in cases of ageing or degenerative lesions, or as a submucosal implant in the urinary tract for urinary incontinence or vesicoureteral reflux. It may also be injected into the vocal cords to treat the effects of paralysis, atrophy, or scarring.	MEDICAL DEVICE
	b) Synovial joint replacement fluid (Joint lubricant)	To help cushion the joint, especially in cases of endogenous synovial fluid reduced viscosity from degenerative disease.	MEDICAL DEVICE

	c) <i>Aqueous/vitreous humour replacement medium</i>	It is used to assist in performing during ophthalmic surgery, e.g. to maintain the shape of the eyeball during the intervention, preserve tissue integrity, protect from surgical trauma, or to function as a tamponade during retinal reattachment.	MEDICAL DEVICE
7	<u>Peritoneal dialysis dialysate</u>	It is used for the exchange of solutes across the peritoneum of the patient (in this case, used as a semi-permeable membrane)	DRUG
8	<u>Haemodialysis dialysate</u>	It is used for the exchange of solutes with blood through a semi-permeable membrane in the dialyser of a haemodialysis system.	MEDICAL DEVICE
9	<u>Fluoride dental preparations</u> a) <i>Oral care product</i>	To maintain oral hygiene.	COSMETIC (If concentration of fluoride is less than or equal to 1500ppm)
		To maintain oral hygiene and prevent oral diseases.	DRUG (If concentration of fluoride more than 1500ppm)
	b) <i>Fluoride dental preparations with a typical device mode of action.</i>	To provide filling to the cavity and provide layer for diseases prevention.	MEDICAL DEVICE
10	<u>Wound treatment product</u> a) comprising a matrix	To administer medicinal product.	DRUG
	b) comprising a matrix	To provide protective layer/ barrier to prevent microbial penetration and create healing environment.	MEDICAL DEVICE
	c) providing a matrix, typically of living cells (fibroblasts) and/or structural proteins	To facilitate the infiltration of native skin elements (e.g., fibroblasts, leukocytes, blood vessels) for skin regeneration.	MEDICAL DEVICE
	d) topical application to a skin wound (e.g. abrasion, laceration, cut, ulcer)	To facilitate local haemostasis primarily through haemoglobin binding. It is available in various forms (e.g. gel, spray, powder, ointment, plaster/ gauze pad) that can be applied directly to the wound where it forms a seal of transparent layer.	MEDICAL DEVICE

	e) topical application to a skin wound	To provide and maintain a moist internal environment for wounds to assist the healing process.	MEDICAL DEVICE
11	<u>Medicated health patch</u>	<ul style="list-style-type: none"> - To relieve fatigue, body aches, joint pains; or - To regulate hormone imbalance 	DRUG
12	<u>Personal Intimate Hygiene Product (Rinse off)</u>	For the female intimate hygiene.	COSMETIC
13	<u>Personal Intimate Lubricant</u>	To use as vaginal lubricants during the climaterium (pre-menopause, menopause, post-menopause) and to treat irritations in vaginal epithelium in cases of physiological decrease of lubrication and consequent increase in vaginal dryness.	MEDICAL DEVICE
		To use for symptomatic relief of vaginal irritation by lowering the pH value.	DRUG
14	<u>Root canal filling incorporating antibiotic</u>	To seal the canal and disinfecting the dentinal walls by diffusing through dentine. The antibiotic provides ancillary actions as bactericidal antibiotic and anti-inflammatory agent to assist in reducing pain and in maintaining a bacteria-free environment within the root canal.	Drug-device combination product regulated as MEDICAL DEVICE
15	<u>Synthetic-fluid tissue reconstructive material</u> (Soft tissue filler incorporating local anaesthetic)	It is used for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds) and local anaesthetic is an ancillary medicinal substance to provide patients with a more comfortable injection experience during procedure.	Drug-device combination product regulated as MEDICAL DEVICE

16	<p><u>General Purpose Surgical Drape</u></p> <p>A sterile protective covering made of natural or synthetic materials, or both</p>	<p>To isolate a site of surgical incision or a surgical field from contamination (e.g., microbial, substance) in various clinical settings (e.g. in an operating room or catheterization laboratory). The device may also be used to protect a patient from heat/ flame during a surgical procedure. This is a reusable or single use device.</p>	<p>MEDICAL DEVICE (If the product/ device did not contain Iodine or contained Iodine < 2%)</p> <p>DRUG (If the product/ device contained Iodine ≥ 2%)</p>
17	<p><u>Wart Cryogenic Kit</u></p> <p>A refrigerant made from dimethyl ether and propane.</p>	<p>To freeze superficial skin lesions (e.g. warts) for their destruction and removal.</p>	<p>MEDICAL DEVICE</p>
18	<p><u>Pressure-ulcer Topical Dressing</u></p> <p>A solution or emulsion designed to be applied to dermal pressure sores.</p>	<p>To prevent and treat pressure/ decubitus ulcers and lower extremity ulcers. It is intended primarily to create a barrier between the skin lesion(s) and the external environment to promote protection and healing.</p>	<p>MEDICAL DEVICE</p>
19	<p><u>Hand Sanitizer</u></p>	<p>For general hand hygiene</p>	<p>COSMETIC</p>

2. DATA EXCLUSIVITY

Data exclusivity refers to protection of undisclosed, unpublished and non-public domain pharmaceutical test data, the origination of which involves a considerable effort, submitted as required to the Director of Pharmaceutical Services for the purpose of scientific assessment in consideration of the:

- a) Quality, safety and efficacy of any new drug product containing a New Chemical Entity
- b) Safety and efficacy for a second indication of a registered drug product as a condition for registration of any new drug product containing a New Chemical Entity; or approval for a Second Indication of a registered drug product.

For information pertaining to Register of Data Exclusivity Granted in Malaysia, please refer: [Register of Data Exclusivity Granted in Malaysia \(New Drug\)](#) and [Register of Data Exclusivity Granted in Malaysia \(Second Indication\)](#)

2.1 HOW TO APPLY

An application for Data Exclusivity (DE) can be made via a [Letter of Intent \(LOI\)](#) in conjunction with the:

- a) Application for registration of a new drug product containing a New Chemical Entity; or
- b) Application for a Second Indication of a registered drug product.

The LOI shall be addressed and submitted manually to the Director of NPCB.

The application must comply with all terms and conditions stated in the directive *Arahan Bagi Melaksanakan Data Eksklusiviti Di Malaysia, Bilangan 2 Tahun 2011*.

The following details are extracted from the Directive on Data Exclusivity (DE) issued by the Director of Pharmaceutical Services under Regulation 29 of the Control of Drugs and Cosmetics Regulations 1984, [Bil \(11\) dlm BPFK/PPP/01/03 Jld 1](#), 28 February 2011.

2.2 APPLICABILITY AND DATE OF COMING INTO FORCE

The directive is applicable to:

- i) New drug product containing a new chemical entity; and
- ii) Second indication of a registered drug product.

New drug product containing any new chemical entity means a product that contains an ¹**active moiety** that has not been registered in accordance with the provisions of the CDCR 1984.

¹**An active moiety** is defined as the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds) or other non-covalent derivative (such as a complex, chelate or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

Second indication for a registered drug product means a single or cluster of therapeutic indications applied subsequent to the first indication(s) approved at the point of registration of the product. The application for approval of the second indication contains reports of new clinical investigations other than bioavailability studies.

The directive shall come into force on **1st March 2011**.

2.3 GRANT OF DATA EXCLUSIVITY

Any person may apply for Data Exclusivity. Such application shall be made upon submission of documents to the Director of Pharmaceutical Services for the:

- a) Registration of a new drug product containing a new chemical entity; or
- b) Approval for second indication of a registered drug product.

An application for Data Exclusivity shall only be considered if the application in Malaysia for:

- a) New drug product containing a new chemical entity is made within eighteen (18) months from the date the product is first registered or granted marketing authorization; AND

Granted Data Exclusivity/ Test Data Protection in the country of origin or in any country, recognized and deemed appropriate by the Director of Pharmaceutical Services.

- b) Second indication of a registered drug product is made within twelve (12) months from the date the second indication is approved; AND
Granted Data Exclusivity/ Test Data Protection in the country of origin or in any country, recognized and deemed appropriate by the Director of Pharmaceutical Services.

Before the Data Exclusivity is granted:

- a) The applicant of a new drug product containing a new chemical entity shall provide to the Director of Pharmaceutical Services the undisclosed, unpublished and non-public domain pharmaceutical test data, the origination, of which involves a considerable effort; OR
- b) The applicant for a second indication of a registered drug product shall provide to the Director of Pharmaceutical Services, the reports of new clinical investigations other than bioavailability studies, conducted in relation to the second indication and the origination of which has involved considerable effort.

The Director of Pharmaceutical Services shall decide on whether the application will be granted the Data Exclusivity. The period of the Data Exclusivity granted shall be made on a case to case basis.

The period of the Data Exclusivity **shall not** be more than:

- a) Five (5) years for a new drug product containing a new chemical entity; and
- b) Three (3) years for a second indication of a registered drug product. The period of Data Exclusivity is for the data concerning the second indication only.

Calculation of the period of Data Exclusivity:

- a) For a new drug product containing a new chemical entity, the period of Data Exclusivity shall be calculated from the date the product is first registered or granted marketing authorization AND granted Data Exclusivity/ Test Data Protection in the country of origin or in any country recognized and deemed appropriate by the Director of Pharmaceutical Services.
- b) For a second indication of a registered drug product, the period of Data Exclusivity shall be calculated from the date the second indication is first

approved AND granted Data Exclusivity/ Test Data Protection in the country of origin or in any country recognized and deemed appropriate by the Director of Pharmaceutical Services.

2.4 CONSIDERATION OF OTHER APPLICATIONS UPON THE GRANT OF DATA EXCLUSIVITY

For a registered new drug product containing a new chemical entity, registration of any other drug product where the active moiety is in all respect the same as the active moiety in the registered drug product which has been granted Data Exclusivity in Malaysia can be considered if:

- a) The applicant provides undisclosed, unpublished and non-public domain pharmaceutical test data, the origination of which involves a considerable effort to demonstrate the quality, safety and efficacy if the drug product submitted for registration; OR
- b) The applicant has obtained consent in writing for right of reference or use of the test data from a person authorised by the owner of the registered new drug product containing a new chemical entity.

2.5 NON-APPLICATION OF DATA EXCLUSIVITY

Nothing in the Data Exclusivity shall:

- a) Apply to situations where compulsory licences have been issued or the implementation of any other measures consistent with the need to protect public health and ensure access to medicines for all; or
- b) Prevent the Government from taking any necessary action to protect public health, national security, non-commercial public use, national emergency, public health crisis or other extremely urgent circumstances declared by the Government.

2.6 APPEAL

Any person aggrieved by the decisions of the Director of Pharmaceutical Services may make a written appeal to the Minister within fourteen (14) days from the date the decision is made known to him and any decision of the Minister made on an appeal shall be final.

A person making an appeal may submit any supporting data or documents to the Director of Pharmaceutical Services not later than:

- a) 120 days for application of new drug products containing any new chemical entity; or
- b) 90 days for the application for second indication of a registered drug product.

3. APPLICATION FORMALITIES

3.1 WHO CAN APPLY FOR PRODUCT REGISTRATION

The applicant for product registration shall be known as the Product Registration Holder (PRH) and must be a locally incorporated company, corporate or legal entity, with permanent address and registered with Companies Commission of Malaysia (with the scope of business related to the health/ pharmaceutical product).

The name of the PRH, including product manufacturer shall not reflect the following:

- a) Name of a government agency;
- b) Name of a research/ institute of higher education;
- c) A name that reflects the quality of pharmaceutical product
e.g. “*Amalan Perkilangan Baik (APB)*”, Good Manufacturing Practice (GMP);
- d) Name of a disease;
- e) Name of an organ.
e.g. Heart, Brain, Kidney etc.

The PRH (if the company is not the product owner) should be authorized in writing by the product owner to be holder of the product registration and be responsible for all matters pertaining to quality, safety and efficacy of the product. This shall include updating any information relevant to the product/ application.

3.2 RESPONSIBILITY OF APPLICANT

- a) To ensure that all transactions with NPCB shall be done by their appointed person(s);
- b) Responsible for all information pertaining to quality, safety and efficacy in support of the product registration application; and shall inform the Authority in a timely manner any change in product information during course of evaluation;

Under the CDCR 1984, Regulation 8(9): Any person who knowingly supplies any false or misleading information to the Authority with his application for the registration of a product commits an offence.

- c) Responsible for all matters pertaining to quality, safety and efficacy of the registered product, including:
 - i. Data updates on product quality, safety and efficacy or current Good Manufacturing Practice (cGMP) compliance of the manufacturers (and repackers, where applicable).

Under the CDCR 1984, Regulation 8(5): Any change in any document, item, sample, particulars or information which shall be notified in writing by the applicant to the Authority within fourteen (14) days from the date of such change.
 - ii. Any decision to withdraw the registration of the product with reasons.
- d) To notify the Authority of any change in correspondence details, including the name, address, contact person, telephone number, fax number and email;
- e) To notify the Authority immediately upon cessation of the applicant as the product registration holder;

3.3 HOW TO APPLY

For registration of products, only web-based online submissions via QUEST at <http://www.bpfk.gov.my> shall be accepted.

To conduct transactions via QUEST system, the applicant must first register a membership for QUEST system with NPCB and purchase a USB Token that contains a User Digital Certificate, from Digicert Sdn. Bhd., which shall be installed to the applicant's computer.

For details, please refer to [Frequently Asked Questions on QUEST System](#).

For charges regarding QUEST USB token, please refer to [Appendix 1: Fees](#).

The applicant shall be responsible for any act of fraudulence or misuse pertaining to its authorized QUEST USB token(s).

The NPCB reserves the rights to approve or reject any application for the QUEST membership.

4. FEES

Under the CDCR 1984, Regulation 8(3): The Authority may charge any applicant such costs as it may incur for the purpose of carrying out any evaluation or investigation prior to the registration of any product.

Any payment made shall **NOT** be **REFUNDABLE** once the application has been submitted and payment confirmed.

Applications without the correct fees will not be processed.

4.1 FEES IMPOSED

Please refer to [Appendix 1](#): Fees for fees imposed, which include:

- a) Charges for USB Token of QUEST Membership;
- b) Processing and Analysis Fee for Product Registration;
- c) Charges for Application of Licence;
- d) Charges for Amendments to Particulars of a Registered Product; and
- e) Fee for Certificates.

4.2 MODE OF PAYMENT

The processing fee and any other charges shall be paid in the form of bank draft/ banker's cheque/ money order/ postal order made payable to "**Biro Pengawalan Farmaseutikal Kebangsaan**".

A separate bank draft/ banker's cheque/ money order/ postal order are required for each application.

5. TYPES OF APPLICATION

5.1 REGISTRATION OF PRODUCTS

5.1.1 APPLICATION FOR PRODUCT REGISTRATION FOR THE FOLLOWING CATEGORIES:

- a) New Drug Products;
- b) Biologics;
- c) Generic;
- d) Health supplements; and
- e) Natural Products.

For details, please refer to [Section A, 1.2 Categories of Product](#) and [Section B: Product Registration Process](#).

5.1.2 REGISTRATION OF COMBINATION PACK (COMBO PACK)

- a) Refers to products which are packed together in combination for a therapeutic regimen such as for the treatment of *Helicobacter Pylori*, Hepatitis C, etc.).
- b) Shall be registered as a single product.
- c) Must consist of registered products only:
 - i. Where a combination pack consists of registered and unregistered products, the unregistered product needs to be registered first, prior to submission of the application;
 - ii. Where a combination pack consists of registered products from different product owners/ PRH, letters of authorization which include product name and product registration number from each product owner shall be submitted.

- d) A product which is packed together with diluent(s)/ adjuvant(s) is NOT considered as a combination pack.
- e) Labelling requirement specifically for combination pack is shown in **Table IV**:

No.	Outer Label	Immediate Label
1.	Name of combination pack	Individual name for each products OR name of combination pack
2.	Registration number for the combination pack	Individual registration number for each products OR registration number for combination pack
3.	Name and address of manufacturer and product registration holder	Name and address of manufacturer and product registration holder
4.	Batch number of the combination pack product	Individual batch number for each products
5.	Expiry date (according to the shortest expiry date from the individual products)	Individual expiry date for each products
<p><u>Note:</u></p> <p><i>These labeling requirements for a combo pack shall as well be subjected to other labelling requirements as stated in Appendix 9.1: Label (mock-up) for Immediate Container, Outer Carton and Proposed Package Insert</i></p>		

5.1.3 REGISTRATION OF PRODUCT FOR EXPORT ONLY (FEO)

- a) Refers to locally manufactured products for export only which are not marketed locally with a different formulation (e.g. colour or strength of ingredients) or shape compared to a registered product;
- b) For products containing ingredients/ formulations which are not allowed by the Authority for local use, applicant shall submit a confirmation in writing from the competent authority of the importing country that there is no objection to the importation and sale of the said ingredients/ formulations. Evidence of registration of the said formulation with the competent authority in importing country may be submitted as supporting data;
- c) Upon application, a Certificate of Pharmaceutical Product (CPP) will be issued to the applicant for the registered FEO products;
- d) For a registered product which is marketed locally and intended to be exported, new registration for export only is NOT necessary if there is no change in the formulation or appearance of the registered product. In this case, a CPP will be issued to the applicant for the registered product, together with an explanation/ declaration letter of any difference(s) to the importing country (e.g. a product exported with a different product name), upon application.
- e) Applications for registration of FEO products are processed based on abridged evaluation.
- f) Applications shall be submitted by using an application form [BPFK 438.1](#) (for Generic Medicines/ Health Supplements) and [BPFK 438.1 \(T\)](#) (for Traditional Products).

5.2 AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

5.2.1 VARIATION

Variation refers to change of particulars of a registered product. No change of any particulars of a registered product shall be made without prior approval from NPCB. The registration of a product shall be reviewed for suspension or cancellation if changes are made without prior approval of the Authority.

There are two types of variation, which are Variation Type I and Variation Type II.

For details, please refer to [Section E: 16.1 Variation.](#)

5.2.2 CHANGE IN MANUFACTURING SITE

Change of Manufacturing Site (COS) refers to change of manufacturing site for certain part or all of the manufacturing process of a product, but it does not cover changes related to a new site, where only:

- a) batch release takes place OR
- b) to a new packager (secondary packaging or labelling), as these changes are covered under applications for amendments to the particulars of a registered product (variation).

However, a change of manufacturing site for biologics shall require a new product application only if the change is extensive that will have an impact on the quality, safety and efficacy profile of the final product.

For details, please refer to [Section E: 16.2 Change of Manufacturing Site.](#)

5.2.3 CHANGE IN PRODUCT REGISTRATION HOLDER

It refers to a transfer of marketing authorization from the existing product registration holder (PRH) to another proposed new holder. This application allows the same registration number of the registered product to be maintained.

For details, please refer to [Section E: 16.3 Change of Product Registration Holder.](#)

5.2.4 NEW/ ADDITIONAL INDICATION

It is defined as an indication which was not initially approved for a registered pharmaceutical product. This shall include new therapeutic indication or indication for a new age group, such as usage in children and shall not include changing/ rephrasing of sentences.

There are two (2) types of evaluation process available for a new/ additional indication application, i.e. full evaluation process and verification process.

For details, please refer to [Section E: 16.4 New/ Additional Indication](#).

5.2.5 APPLICATION FOR A CONVENIENT PACK

- a) Refers to products which are packed together in a single packaging unit for convenience of the consumers, such as a Confinement Set or *Set Jamu Bersalin*.
- b) Shall consist of registered products only.
- c) Applicable to health supplements and natural products only.
- d) Application for a convenient pack shall be made via the variation process.

For details, please refer to [Section E: 16.1 Variation](#) and [Section E: 16.5 Application for a Convenient Pack](#).

5.3 RENEWAL OF PRODUCT REGISTRATION

The registration shall be valid for five (5) years or such a period as specified in the registration certificate (unless sooner suspended or cancelled by the Authority);

The renewal of product registration should be done not later than 6 month prior to expiry together with appropriate fee.

Please refer also at [Section E: 14 Maintenance of Registration](#).

5.4 CERTIFICATES

5.4.1 CERTIFICATE OF PHARMACEUTICAL PRODUCT (CPP)

A CPP which follows the format recommended by WHO shall be issued to locally manufactured products that are to be exported. For application of CPP, applicant shall fill in form [BPFK 412.2](#): *Permohonan Perakuan Keluaran Farmaseutikal*.

A fee, as stated in [Appendix 1: Fees](#), is payable on the issue of such certification.

Upon receipt of complete application, the certificate shall be issued within fifteen (15) working days.

5.4.2 GOOD MANUFACTURING PRACTICE (GMP) CERTIFICATE

According to the CDCR 1984, compliance to Good Manufacturing Practice (GMP) is prerequisite to application of a manufacturing license, as well as product registration/cosmetic notification.

GMP is a standard which shall be followed by the manufacturers to ensure that the products manufactured are safe, efficacious and of quality.

Upon complete application, a GMP certificate will be issued and a fee, as stated in [Appendix 1: Fees](#), is payable on the issue of such certification.

If a manufacturer who wishes to build a new manufacturing premise, the manufacturer may submit a proposed premise layout plan to the Centre for Compliance and Licensing, NPCB for evaluation.

For more information, please refer [Section D: 13.4 GMP Certificate](#) and/or [NPCB website](#).

5.5 LICENSES

Note:

In addition to the relevant laws and regulations as stated in this DRGD, manufacturers are required to comply with the principles of Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP). Meanwhile, Importers and Wholesalers are required to comply with the principles of Good Distribution Practice (GDP).

According to the CDCR 1984, any company who wishes to manufacture, import and/or wholesale any registered products needs to have Manufacturer's Licence, Import Licence and/or Wholesaler's License.

For more information pertaining application of appropriate licences, please refer [Section D: 13. Licensing](#) or contact Licensing Unit, Centre for Compliance and Licensing (CCL), NPCB or [NPCB website](#).

As for processing fee for these applications, please refer to [Appendix 1: Fees](#)

5.6 CLINICAL TRIAL IMPORT LICENCE (CTIL)/ CLINICAL TRIAL EXEMPTION (CTX)

For more information pertaining to any matters of [clinical trial](#), please refer to NPCB website.

6. GENERAL CONDITIONS FOR REGISTRATION OF DRUG PRODUCTS UNDER THE CONTROL OF DRUGS AND COSMETICS REGULATIONS 1984

6.1 REGISTRATION NUMBER

The product registered with the Registration Number as stated in the Registration Certificate shall have the name, composition, characteristics, specifications and origin as specified in the registration documents.

Registration number appears as MALYYMM\$\$\$\$@##, e.g. MAL11070001ACERS:

- MAL refers to "Malaysia"
- YYMM refers respectively to year and month of registration by the Authority (e.g. 1107: July 2011);
- \$\$\$\$ refers to a serial number for a product being registered (e.g. 0001);
- @ refers to category of product being registered i.e. A/ X/ N/ T/ H; and
- ## refers to administrative code used by NPCB i.e. C/ E/ R/ S.
- The symbols @ and ## refer to:
 - a) A= Scheduled Poison
 - b) X= Non-scheduled Poisons
 - c) N= Health Supplements
 - d) T= Natural Products/ Traditional Medicines
 - e) H= Veterinary Products
 - f) C= Contract Manufactured (the product is manufactured by a GMP certified contract manufacturer)
 - g) E= For Export Only (FEO) (the product is to be sold for export only and not for sale in the local market)
 - h) R= Repacked (the product is repacked by an approved GMP certified repacker)
 - i) S= Second source (the product from a second source/ approved second manufacturer)

6.2 PRODUCT PARTICULAR

The holder of the registration certificate shall supply such documents, items, samples, particulars or information as the Authority may require in relation to the registered product.

No change in name, composition, characteristics, origin, specifications, manufacturer, packing, indications, labeling, package insert, product literature or any relevant particulars of the registered product shall be made without prior approval of the Authority.

6.3 LABELLING

The registered product shall be labeled with the Registration Number. The labels for the registered product shall comply with all other labeling requirements specified by the Authority.

6.4 PRODUCT AUTHENTICATION

The registered product shall be affixed with the security device approved by the Authority. The said security device (hologram), which is serialized, shall be used to authenticate and verify that the product is registered with the Authority, and will be affixed to each unit pack of the product, whether locally manufactured or imported.

The security device shall be affixed onto the outer packaging of the product, (or, where there is no outer packaging, on the immediate packaging), on the front panel of the product label. None of the product particulars on the label shall be covered over by the security device.

Please refer to:

- a) [Appendix 9](#): Labelling Requirements where the security device/ label may be affixed on the product label;
- b) [FAQ](#) no. 20 on hologram; and
- c) Circulars and directives pertaining to security label (hologram):
 - i) [Bil \(32\) dlm BPFK/02/5/1.3](#)
 - ii) [Bil \(36\) dlm BPFK/02/5/1.3](#)
 - iii) [Bil \(62\) dlm BPFK/02/5/1.3](#)
 - iv) [\(88\)dlm.BPFK/PPP/01/03 Jilid 2](#)
 - v) [\(1\)dlm.BPFK/PPP/07/25 Jld. 1](#)

6.5 INDICATIONS, SPECIAL CONDITIONS

The registered product shall only be indicated for use as approved by the Authority. The importation, manufacture, sale and supply of the registered product shall comply with all other specific conditions imposed by the Authority.

6.6 ADVERSE REACTIONS, COMPLAINTS

The product registration holder or any person who possesses any registered product shall inform the Senior Director of Pharmaceutical Services immediately of any adverse reactions arising from the use of the registered product.

6.7 HOLDER OF REGISTRATION CERTIFICATE

The holder of the registration certificate shall inform the Authority of any change in his name or address.

6.8 WITHDRAWAL FROM REGISTRATION

The holder of the registration certificate shall notify the Authority with regards to any decision to withdraw registration of a product and shall state reasons for the decision.

The holder shall also notify the Authority when he is no longer authorized to be the holder of the registration certificate.

Upon withdrawal, the registration certificate is no longer valid.

6.9 CANCELLATION, SUSPENSION, AMENDMENT BY THE AUTHORITY

The Authority may, at any time and without assigning any reason suspend or cancel the registration of any product, and may amend the conditions of registration. The holder of the registration certificate shall immediately surrender to the Authority the registration certificate upon cancellation or suspension of the registration of the product.

The Authority may, at any time and without assigning any reason suspend or cancel the registration of any product, and may amend the conditions of registration, upon which the registration certificate is no longer valid.

6.10 DIRECTIVES

The Senior Director of Pharmaceutical Services may issue written directives or guidelines to any person or a group of persons as he think necessary for the better carrying out of the provisions of these Regulations and which in particular relate to:

- a) Product quality, safety and efficacy;
- b) Labeling;
- c) Change of particulars of a product;
- d) Transfer of licenses;
- e) Manufacturing;
- f) Storage includes requirements as to containers;
- g) Retailing;
- h) Promotion of sale including product information;
- i) Product recall;
- j) Product disposal;
- k) The cost of product recall or product disposal;
- l) Clinical trials; or
- m) Records and statistics pertaining to manufacture, sale, supply, import or export of any products.

7. USE OF *HALAL* LOGO

Halal logo may be used voluntarily on registered product label for the following categories, for both local and export market, provided that such products have been certified and approved *halal* by the Malaysia Department of Islamic Development (*Jabatan Kemajuan Islam Malaysia*, JAKIM):

- a) Non-scheduled poison, excluding parenteral dosage form and veterinary products;
Reference: Circular [\(95\)d/m.BP/PP/01/03 Jld. 2](#)
- b) Health supplements;
- c) Natural products; and
- d) Cosmetics.

However, the logo is **NOT** allowed to be used on label of registered products other than the categories as listed above.

Only *halal* logo issued by JAKIM or any Islamic Body which is recognized by JAKIM shall be accepted.

Consideration by the Authority for use of *halal* logo on product label of such products shall be based on application as it is not a mandatory requirement.

Applicant shall submit application for [variation type II](#) to NPCB for approval to affix *halal* logo on product label of a registered product of which a *halal* certification has been granted. A copy of the *halal* certificate must be submitted as a supporting document.

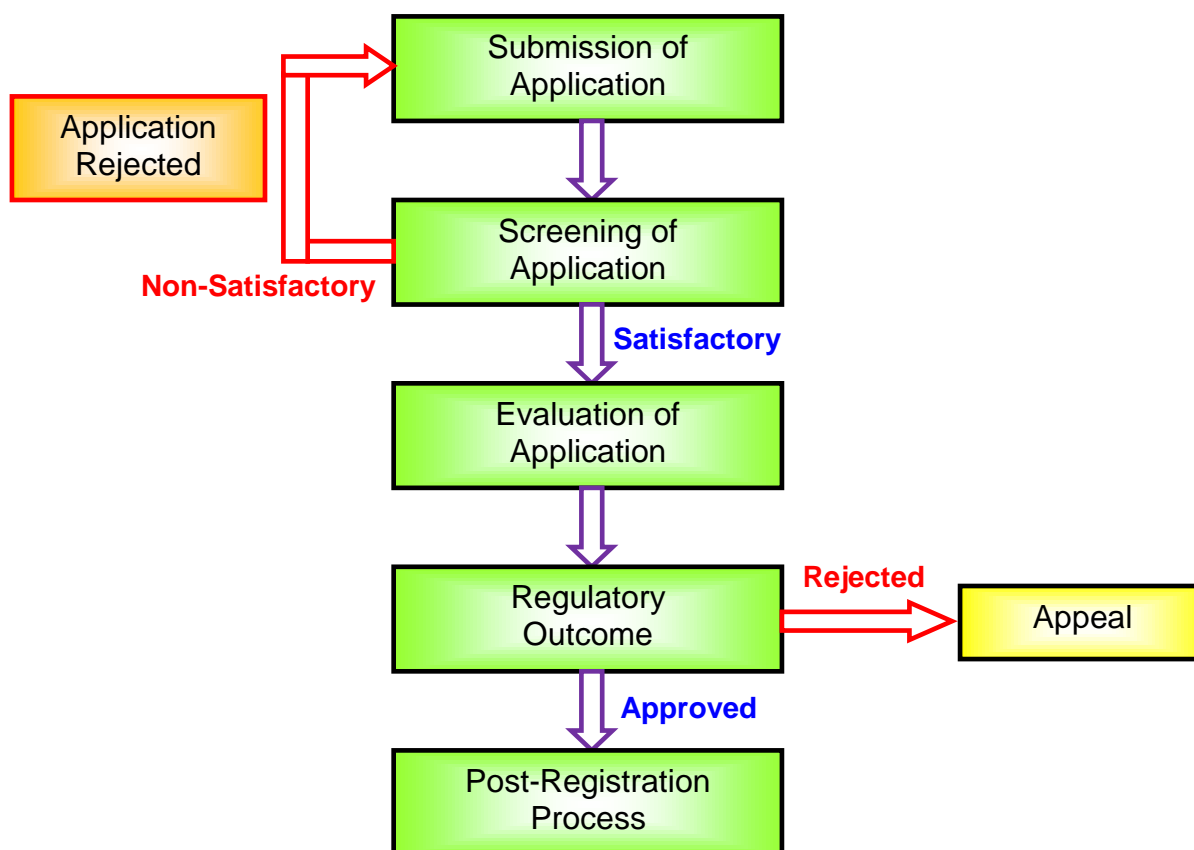
SECTION B: PRODUCT REGISTRATION PROCESS

The process of product registration ensures that pharmaceutical products are evaluated for its safety, efficacy and quality, whereas natural products are evaluated for its safety and quality, prior to being registered by the Authority and finally released into the market.

8. FLOW OF REGISTRATION PROCESS

Figure 4:

Process of Product Registration



8.1 PRE-SUBMISSION OF APPLICATION

Prior to submission of an application for product registration, applicant shall determine/ understand:

- a) The category of the product (different product category requires different data);
- b) Method of evaluation;
- c) General and specific requirements;
- d) Conditions applied;
- e) Multiple applications;
- f) Variants; and
- g) Language.

A product shall only be registered if it fulfills regulatory requirements imposed by the Authority, especially **with respect to quality, efficacy and safety** of the product and taking into consideration on the following criteria:

- a) Necessity of the product;
- b) Potential for abuse; and
- c) Therapeutic advantages.

8.1.1 CATEGORY OF PRODUCT

Applicant shall determine on the category of a product, as described under [Section A - General Overview](#).

If the product category is uncertain, applicant may submit a [Classification Form](#) to Section of Regulatory Coordination, Centre for Product Registration, NPCB for verification.

8.1.2 METHOD OF EVALUATION

Method of evaluation for registration of a product is divided into two (2) types, which are:

- a) Full Evaluation; and
- b) Abridged Evaluation.

Table V: Method of Evaluation According to Product Categories

No.	Product Category	Method of Evaluation	
		Full Evaluation	Abridged Evaluation
1.	New Drug Products	√	Not Applicable
2.	Biologics	√	Not Applicable
3.	Generics (Scheduled Poison)	√	Not Applicable
4.	Generics (Non-Scheduled Poison) [or known as OTC]	* All products from this category, unless stated in Abridged Evaluation	Includes, but not limited to the following: <ul style="list-style-type: none"> • Antiseptics/ skin disinfectants; • Locally-acting lozenges/ pastilles; • Topical analgesic/ counter-irritants; • Topical nasal decongestants; • Emollient/ demulcent/ skin protectants; • Keratolytics; • Anti-dandruff; • Oral care; • Anti-acne; • Medicated plasters/ patch/ pad; and • Topical antibacterial.
5.	Health Supplements a) General or Nutritional Claims	Not Applicable	√
	b) Functional Claims (Medium)	Not Applicable	√
	c) Disease Risk Reduction Claims (High)	√	Not Applicable
6.	Natural Products	Not Applicable	√

* **Table VI:****Products containing Glucosamine, Chondroitin and Methylsulphonylmethane (MSM)**

No.	Product		Product Category	Route of Evaluation	Condition on Product Indication	Remark
1.	Products containing Glucosamine	As single active ingredient	OTC	Full evaluation	As adjuvant therapy for osteoarthritis	As combination with other supplement ingredients are NOT allowed to be registered
		As combination with Chondroitin and/or MSM	OTC	Full evaluation	As adjuvant therapy for osteoarthritis	
2.	Products containing Chondroitin	As single ingredient OR In combination with other supplement ingredients	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-
3.	Products containing MSM	As single ingredient OR In combination with other supplement ingredients	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-
		As combination with Chondroitin	Health supplement	Abridged Evaluation	No therapeutic claims are allowed	-

Reference: Circular [Bil \(66\) dlm BPFK/02/5/1.3](#)

8.1.3 REQUIREMENTS FOR PRODUCT REGISTRATION

Applicant shall submit the following requirements to support an application for product registration, applicable according to different category of product:

a) General requirements (either for full or abridged evaluation);

i) Full Evaluation;

(In accordance to ASEAN ACTD/ ACTR or ICH guidelines)

- Part I - Administrative data and product information;
- Part II - Data to support product quality (Quality Document);
- Part III - Data to support product safety (Nonclinical Document); and
- Part IV - Data to support product safety and efficacy (Clinical Document).

OR

ii) Abridged Evaluation.

For details, please refer [Appendix 2: Requirements for Product Registration](#).

b) Specific requirements according to category of product (biologics, health supplements and natural products).

- Biologics : Refer [Appendix 3: Guideline on Registration of Biologics](#)
- Health : Refer [Appendix 4: Guideline on Registration of Health
supplements Supplements](#)
- Natural : Refer [Appendix 5: Guideline on Registration of Natural
products Products](#)

For regulatory control of active pharmaceutical ingredient (API), it is applicable to all pharmaceutical products either locally manufactured or imported, excluding biologics, health supplements and natural products.

The [implementation](#) has begun with voluntary submission for New Drug Product (NDP) in April 2011 and followed by;

- Phase 1 - New Drug Products (NDP) (mandatory in Jan 2012)
- Phase 2 - Generics (Scheduled Poison) (to be determined)
- Phase 3 - Generics (Non-scheduled Poison) (to be determined)

No separate application for registration of the API is required. However, the required technical documentation pertaining to each API at Part 2.S ACTD (Part II Quality: Drug Substance) shall be submitted as part of the application for product registration.

For details pertaining to regulatory control of API, please refer [Appendix 6: Guideline on Regulatory Control of Active Pharmaceutical Ingredients \(API\)](#).

8.1.4 CONDITIONS APPLIED ON PRODUCT REGISTRATION

Applicant shall comply with the following conditions applied on product registration. Failure to do so shall result in rejection of the application by the Authority.

- a) Applicant shall comply with all requirements as specified in the following appendices and directions from the Authority:
 - i) [Appendix 7:](#)
Special Conditions for Registration for a Particular Product or Group of Products;
 - ii) [Appendix 8:](#)
List of Permitted, Prohibited and Restricted Substances;
 - iii) [Appendix 9:](#)
Labelling Requirements;
 - iv) [Appendix 10:](#)
Guideline on Patient Dispensing Pack for Pharmaceutical Products in Malaysia
(Applicable to pharmaceutical products only).
- b) Applicant shall provide supplementary data/ information, documentation or samples, if requested by the Authority;
- c) Applicant shall respond and provide feedback for the requested supplementary data/ information, documentation or samples by the Authority within the specified timeframe. If the applicant is unable to submit the requirements within the specified timeframe, a written request for an extension shall be submitted to NPCB;
- d) Application shall be rejected if the applicant fails to submit required supplementary data/ information, documentation or samples within six (6) months from the first correspondence date;
(Reference: Circular [Bil \(08\) dlm. BPFK/PPP/01/03](#))

- e) Applicant shall submit sample of natural product for laboratory testing to the Centre for Quality Control, NPCB within fourteen (14) days from date of confirmed payment. Failure to do so within thirty (30) days from the date of the payment shall result in rejection of the application;

8.1.5 MULTIPLE APPLICATIONS

Separate application for product registration shall be required for each product for the following conditions:

- a) Products containing the same ingredients but made to different specifications, in terms of strength/ content of ingredient(s), dosage form, description, etc.; or
- b) Different manufacturer.

However, different packings (materials) or pack sizes (quantity/ volume) of a product made by the same manufacturer to the same specifications, formulation and dosage form (including parenteral preparations, peritoneal dialysis fluids and haemofiltration solutions which are introduced into human bodies) shall require only one application for product registration. The product registration shall be for the packings and pack sizes stated in the registration documents only.

Note:

Registration of same product in all aspects but with different product name by the same PRH is not allowed by the Authority.

8.1.6 SECOND OR THIRD SOURCE

It is defined as product which is the same as the product from first source in all aspects, except for the site of manufacture.

An application for a second source may be considered by the Authority but only with justification.

A second source product, excluding biologic products, may differ for the following aspects:

- a) equipments/ machines;
- b) minor manufacturing process (e.g. blending time, number of sub-parts);

- c) batch size;
- d) packaging materials, thickness of same packaging materials, pack sizes;
(Note: Use of different packaging material shall be supported with stability study report.)
- e) manufacturer of API; and
- f) source of excipients;

EXCEPT differences in shape, embossment and thickness of tablet, in order to avoid change in product identity and subsequently causing confusion.

The manufacturer shall declare with support of manufacturing validation process data that there is no change in formulation, specification of active ingredient(s) and excipient(s), and finished product for the second source product compared to the first source.

For pharmaceutical product, no third source is allowed for same product unless in emergency situation such as outbreak of infectious disease.

For biologics, a third source may be considered if justified.

8.1.7 VARIANTS

Variants refer to products with differences in terms of fragrance/ flavour or consequently colour.

When variants are registered:

- a) The variants should only differ in terms of fragrance/ flavour and colour.
- b) Product name of the variants shall remain the same, with the addition of an identifying variant name.
- c) Each variant shall be registered as one (1) product with a different registration number.

A maximum of **five (5) variants** to the registered product may be considered for the following dosage forms:

- a) Products Containing Scheduled Poison
ONLY for pediatric oral liquid preparations
- b) Products Containing Non-Scheduled Poison
 - i) Lozenges;
 - ii) Chewable tablets;

- iii) Effervescent powders/ tablets;
- iv) Powder;
- v) Granule;
- vi) Oral liquid;
- vii) Dental preparations (rinses, dentifrices);
- viii) Medicated soaps (bar, liquid); and
- ix) Vaginal creams and douches.

8.1.8 LANGUAGE

All data and information including supporting documents for product registration such as certificates, letters and product labels shall be in English or *Bahasa Malaysia*.

8.2 SUBMISSION OF APPLICATION

Application of product registration shall be submitted via the online QUEST system at www.bpfk.gov.my.

Applicant shall ensure all data requirements needed to support the application is fulfilled before submission.

Upon submission, the application shall be given a call number for reference, which is specific to a particular product. Applicant shall refer to this call number during all correspondence pertaining to the registration of the product.

Applicants are advised to read the explanatory notes as stated in [Appendix 11](#): Guideline on Filling the Online Application Form for Product Registration via Quest System, and also relevant ASEAN or ICH guidelines and checklists, for full information on requirement for product registration.

8.3 SCREENING OF APPLICATION

After an online submission of the product registration application has been done, the application shall be undergone an initial evaluation (or known as screening process) which shall ensure the required data/ information of the submitted application are complete. Further evaluation shall be done after payment for the application has been made.

8.3.1 SATISFACTORY

Only a complete application shall be accepted and approved for payment. Upon screening approval, the applicant is requested to proceed for payment and submission of hard copy documents (if applicable).

Submission of hard copy documents:

No.	Category of Product	Online Submission	Hard copy submission
1.	NDPs	All documents as required under Part I – IV	<ul style="list-style-type: none"> - A copy of CD and a copy of documents as required under Part I – IV; - Nine (9) copies of indexed folders containing proposed package insert and published clinical papers and/or in-house synopses; - A copy of CD and a copy of documents as required under Appendix 6, Table 1 (<i>for drug substance/ API</i>); - Further documentations may be requested from case-to-case as deemed necessary.
2.	Biologics	All documents as required under Part I – IV	Part I – IV including published clinical papers (6 sets – indexed, listing with summary/ abstracts of each paper)
3.	Generics (Scheduled Poison)	All documents	As requested e.g. big file size, unable to be submitted online
4.	Generics (Non-Scheduled Poison)	All documents	As requested e.g. big file size, unable to be submitted online

No.	Category of Product	Online Submission	Hard copy submission
5.	Health Supplements	All documents	As requested e.g. big file size, unable to be submitted online
6.	Natural Products	All documents	All Sections (Section A-F) Ref.: Circular (103) dlm.BPFK/PPP/01/03Jilid 2

For payment, applicant shall submit two (2) copies of printed payment voucher together with appropriate fees to the Finance Department, NPCB for payment confirmation. The applicant is advised to keep a copy of the payment voucher as reference. A product reference number shall be given to the application upon payment confirmation.

Payment has to be made within thirty (30) days from the date of approval for screening. The application form will be deleted from the system if payment has not been made within this stipulated time.

8.3.2 NON-SATISFACTORY

If the application is found incomplete during the screening process, the application shall be rejected and the applicant shall be notified via the system.

Note:

If there is any decision made by the applicant/ required by the Authority in certain cases to withdraw a submitted application for registration of a product, at any stage of evaluation prior to its approval, the applicant shall notify the Authority and shall state the reasons for the decision.

8.4 EVALUATION OF APPLICATION

8.4.1 INITIATION OF REVIEW

Upon confirmation of payment, the application with the submitted data shall be evaluated. Review of applications shall follow a queue system. There shall be separate queues for the different categories of products and/or according to level of claims i.e. general, medium or high claim.

Priority review may be granted for product which is intended for treatment of a serious or life-threatening disease, where the likelihood of death is high unless the course of the disease is interrupted.

8.4.2 CORRESPONDENCE

Correspondence via the system shall be sent to the applicant if there is any clarification and further supplementary data/ information, documentation or samples pertaining to the application, if deemed necessary by the Authority.

Application shall be rejected if the applicant fails to respond to the correspondence from NPCB to submit the required supplementary data/ information, documentation or samples within six (6) months from the first correspondence date. (Reference: Circular [Bil \(08\) dlm. BPFK/PPP/01/03](#))

8.4.3 STOP CLOCK

Under review.

8.4.4 TIMELINE FOR PRODUCT REGISTRATION

Table VII:

No.	Product Category	* Duration (Inclusive screening process)
(A)	Full Evaluation	
1.	New Drug Products	245 working days
2.	Biologics	245 working days
3.	Generics (Scheduled Poison)	210 working days
4.	Generics (Non-Scheduled Poison)	210 working days
(B)	Abridged Evaluation	*Duration (Inclusive screening process)
5.	Generics (Non-Scheduled Poison) (Product categories as stated in Table V above)	80 working days
6.	Natural Products a) Single active ingredient b) Two (2) or more active ingredients	a) 116 working days b) 136 working days
7.	Health Supplements a) ** Single active ingredient b) ** Two (2) or more active ingredients ** <i>Applicable for:</i> i) <i>General or Nutritional Claims; and</i> ii) <i>Functional Claims (Medium Claims)</i> c) Disease Risk Reduction Claims (High Claims)	a) 116 working days b) 136 working days c) 245 working days

* Upon receipt of complete application.

8.5 REGULATORY OUTCOME

8.5.1 DECISIONS OF THE AUTHORITY

A regulatory decision shall be made based on the outcome of the evaluation of the submitted documentation, and samples (if applicable). An application may be approved or rejected by the Authority, and the Authority decision will be sent via email/ official letter to the product registration holder.

As stipulated under the CDCR 1984, Regulation 11(1), the Authority may, at any time reject, as well as cancel or suspend the registration of any product if there are deficiencies in safety, quality or efficacy of the product or failure to comply with conditions of registration.

8.5.2 PRODUCT REGISTRATION NUMBER

As stipulated in Regulation 8(8), CDCR 1984, upon registration of a product by the Authority, the product registration holder shall be notified by the Authority and a product registration number (i.e. MAL number) shall be assigned to the registered product via the system.

The registration number is specific for the product registered with the name, identity, composition, characteristics, origin (manufacturer) and product registration holder, as specified in the registration documents. It shall NOT be used for any other product.

8.5.3 CERTIFICATE OF REGISTRATION

Form 1 (Certificate of Registration) for a product with the provisions, conditions, limitations and etc. of the registration, as stipulated in Regulation 8(8) of CDCR 1984, has been deleted from the regulation in year 2006 via amendment of PU(A) 336/06. Therefore, the certificate will no longer be issued by the Authority.

Applicant shall refer to the product registration approval notification sent by the Authority or the [Approved Product Registration List](#) in NPCB website.

Reference: [Circular \(100\)d/m.BPFK/PPP/01/03 Jld. 2](#)

8.6 POST-REGISTRATION PROCESS

Registration status of a product shall be valid for **five (5) years** or such period as specified in the registration certificate (unless the registration is suspended or cancelled by the Authority).

Upon approval for product registration by the Authority, applicants shall fulfill all commitments and conditions imposed during approval of the product registration and shall be responsible for the maintenance of the product in terms of quality, safety and efficacy throughout the validity period of registration. Failure to do so may result in rejection of application for renewal of product registration.

The Authority shall be notified of any changes to the product's efficacy, quality and safety, as described in detail at [Section E: Post-Registration Process](#).

8.7 REJECTED APPLICATION

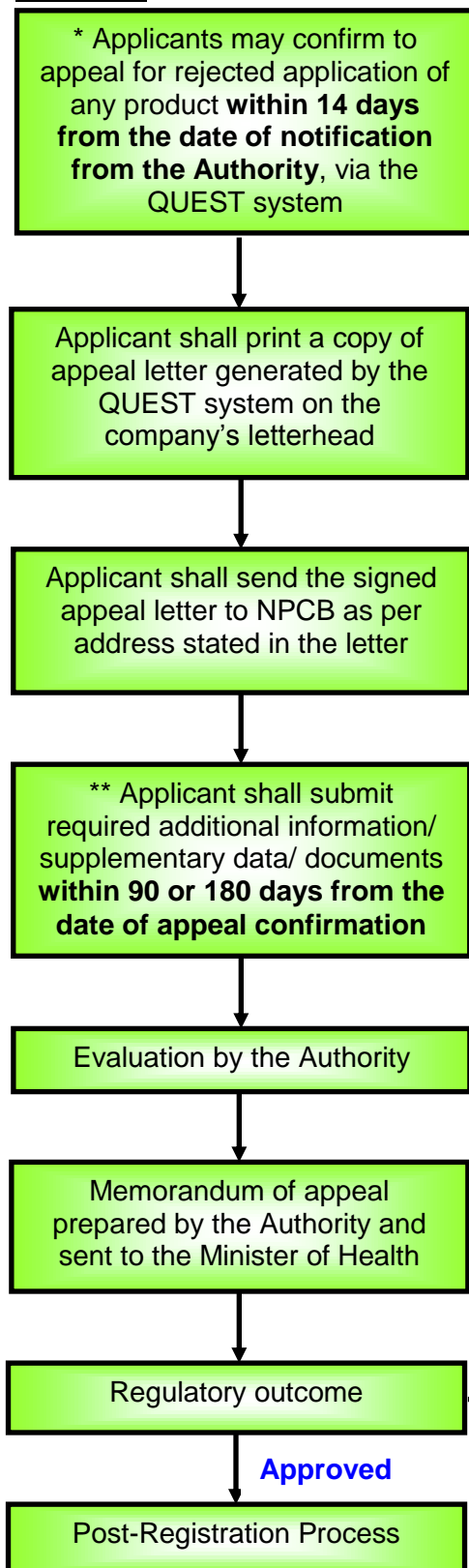
As stipulated in Regulation 18, CDCR 1984:

- a) Any person aggrieved by the decision of the Authority or the Director of Pharmaceutical Services, a written appeal may be made to the Minister of Health Malaysia;
- b) **All notice of appeals** shall be made **within fourteen (14) days** from the date of notification from the Authority;
 - A period of 180 days from the date of notice of appeal is given for submission of any additional information/ supplementary data/ documents for New Drug Products and Biologics.
 - A period of 90 days is allowed for other categories of product.
 - The appeal shall not be considered if all the required information is not submitted within the specified timeframe given. **Any request for extension of this period shall not be considered too.**
- c) Any decision of the Minister made on an appeal shall be final.

Re-submission for product registration of a rejected application due to reason of safety and efficacy shall not be accepted within **two (2) years** after the rejection. However, if the product is registered in the reference countries, submission of application can be made earlier.

8.7.1 PROCESS OF APPEAL FOR QUEST 2 PRODUCT

Figure 5:



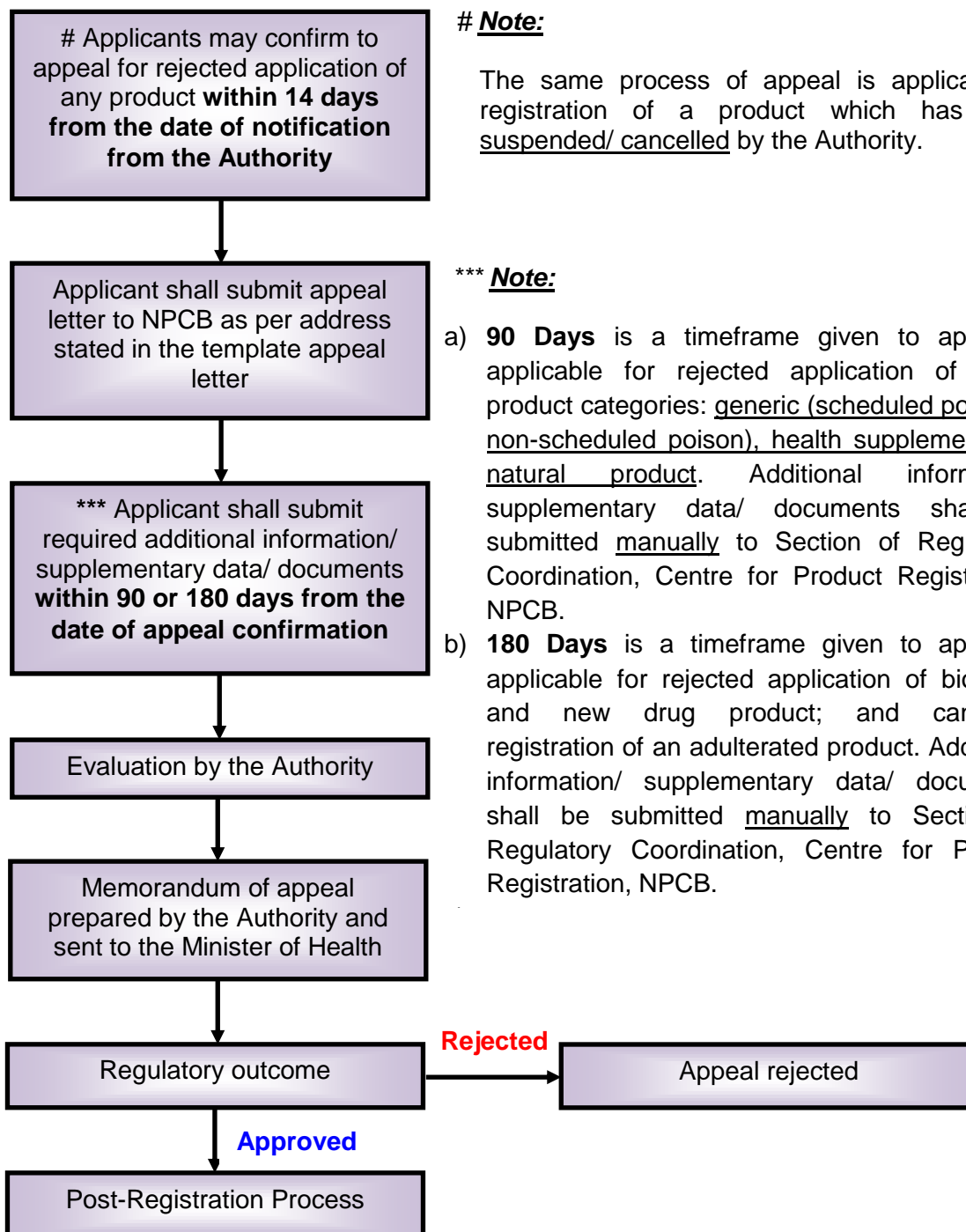
*** Note:**

For suspended/ cancelled registration of a product, applicant may confirm to appeal manually by sending an appeal letter to NPCB **within fourteen (14)** days from the receipt of notification letter from the Authority, and it shall be subjected to the same process of appeal.

- a) **** 90 Days** is a timeframe given to applicant applicable for rejected application of these product categories: generic (scheduled poison & non-scheduled poison), health supplement and natural product. Additional information/ supplementary data/ documents shall be submitted via QUEST system.
- b) **** 180 Days** is a timeframe given to applicant applicable for rejected application of new drug product and biologics; and cancelled registration of an adulterated product. Additional information/ supplementary data/ documents shall be submitted manually to Section of Regulatory Coordination, Centre for Product Registration, NPCB.

8.7.2 PROCESS OF APPEAL FOR QUEST 3 PRODUCT

Figure 6:



8.7.3 TEMPLATE FOR AN APPEAL LETTER

LETTERHEAD SYARIKAT PEMEGANG PENDAFTARAN PRODUK

Nama dan alamat pemegang

Tarikh:

Y. B. Menteri Kesihatan Malaysia

d/a Biro Pengawalan Farmaseutikal Kebangsaan
Kementerian Kesihatan Malaysia
Jalan Universiti, Peti Surat 319,
46730 Petaling Jaya
(u.p. Setiausaha PBKD)

Y. B.,

**PERATURAN 18 – RAYUAN TERHADAP PENOLAKAN PERMOHONAN
PENDAFTARAN**

NAMA PRODUK : Sila nyatakan nama produk (*Please state the product name*)
NO. RUJUKAN : Sila nyatakan nombor pendaftaran produk
(*Please state reference number of the product*)

Dengan segala hormatnya, pihak kami ingin membuat rayuan terhadap penolakan permohonan produk seperti di atas.

2. Alasan – alasan rayuan serta data tambahan/ maklumat akan dihantar kepada pihak Y.B. dalam tempoh *90 hari / 180 hari dari tarikh surat ini dikeluarkan.

Sekian, terima kasih.

Yang benar,

Tandatangan Wakil Pemegang

(NAMA WAKIL PEMEGANG)

Jawatan Wakil Pemegang

* Potong mana-mana yang tidak berkaitan.
(*Please cross out words that do not apply.*)

SECTION C: QUALITY CONTROL

The requirement for the submission of the protocol of analysis (POA), analytical method validation (AMV) and product samples for laboratory testing are presented in this section.

The submission of POA and AMV to the Centre for Quality Control shall be done via the online system (Quest system) and also using hardcopies, once payment for the registration has been confirmed. Documents to be submitted are listed below:

Documents to be submitted via online Quest system

1. E9 : Complete protocol of analysis for finished product including preservatives and diluents (if any).
2. E10 : Summary of AMV which includes all the relevant validation characteristics, its acceptance criteria and results.
3. E11 : Certificate of analysis for active drug substance (1 batch) and recent batches of finished product (3 different batches).

Documents to be submitted as hardcopy:

1. Certificate of analysis for active drug substance (1 batch) and recent batches of finished product (3 different batches)
2. Complete protocol of analysis for active drug substances and finished product (including preservatives and diluents, if any)
3. Complete testing method for the AMV.
4. Complete results for the AMV with all relevant validation parameters, including acceptance criteria and supporting raw data (e.g. chromatograms, spectrums etc.)

Note:

1. A cover letter consisting of the following information should be enclosed with every hard copy document submission:
 - i) Name of product;
 - ii) Reference Number/ Protocol Number;
 - iii) Contact person (name/ email address/ telephone no.);
 - iv) Name and address of company.
2. Documents submitted should be well organized and indexed.

9. GUIDELINE FOR THE SUBMISSION OF PROTOCOL OF ANALYSIS (POA)

This guideline consists of general and specific requirements for the POA submission. The general requirements are referred to POA content whilst details of the test methods are illustrated in the specific requirements

9.1 GENERAL REQUIREMENTS

- a) The POA shall be written in *Bahasa Malaysia* or English only.
- b) The POA shall contain the following information:
 - i) Name of product;
 - ii) Name and address of manufacturer;
 - iii) Name, signature and designation of authorized person;
 - iv) Effective date and Review date.
- c) The POA shall comply with the following requirements :
 - i) To provide updated testing methods, shelf-life specifications and certificate of analysis for the intended product to be registered.
 - ii) References used must be clearly stated.
 - iii) The latest version of British Pharmacopoeia (BP) and United State Pharmacopoeia (USP) shall be used as the main references.
 - iv) All tests and its specification listed in BP and/or USP shall be the minimum requirement. However, a specific testing method for quantitative analysis shall be accepted.
 - v) All test specifications set by the manufacturer shall be in line or more stringent than official pharmacopoeias (BP and USP).
- d) Details of test methods shall include the following items:
 - i) List of equipment and apparatus;
 - ii) List of chemical, reagents and media;
 - iii) Preparation of solutions such as sample, standard, mobile phase, medium etc.;
 - iv) Setting up of analytical instrumentation;
 - v) System suitability tests (resolution, percentage of Relative Standard Deviation (%RSD), tailing factor and theoretical plate for High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) methods);
 - vi) Complete formula for calculation and interpretation of results;

- vii) Specification or acceptance criteria.
- e) Photocopies or methods directly copied from pharmacopoeias shall not be accepted. In cases where test methods are adopted from official pharmacopeia, details of specifics requirements should be submitted.
- f) All relevant data collected during chemical and microbiological testing such as chromatograms HPLC/ GC, test reports and formulae used for calculating should also be submitted.
- g) All documents should be arranged and labeled accordingly.

9.2 SPECIFIC REQUIREMENTS

The specific requirements for test methods are based on type of tests and dosage forms of product as stated in **Table VIII** below:

Categories	Type of Tests	Specific Requirements
Physical & Performance Tests	Physical test (friability, uniformity of weight, pH, etc)	Specific method for the intended analysis
	Disintegration test	Specific method for related dosage forms
	Dissolution test	<p>a. Dissolution parameters should include:</p> <ul style="list-style-type: none"> i) type of apparatus ii) type and volume of dissolution medium iii) rotation rate iv) temperature of solution v) sampling time <p>b. Complete formula for calculation especially for extended and delayed release products.</p> <p>c. Method of analysis for example HPLC, UV, etc.</p>

Categories	Type of Tests	Specific Requirements
Quality Test	Identification test such as color test, Fourier Transform Infrared (FTIR), Thin Layer Chromatography (TLC) etc.	Specific method for the intended analysis
	Impurities/ degradation/ purity test	a. Analysis method should include:- i) Placebo solution (if any) ii) Relative retention times of impurities or degradation product b. Complete formula for calculation c. Method of analysis for example HPLC, TLC, etc.
	Assay and uniformity of content	Specific method for the intended analysis
	Biological Assay of Antibiotics	a. Procedure for preparation of following solutions/ substances:- i) Culture medium ii) Buffer solutions iii) Diluents iv) Microorganisms used in assay b. Detailed test method (diffusion or turbidimetric method), which includes: i) Preparation of standard solutions (including steps to counteract the antimicrobial properties of any preservatives, etc present in the sample) ii) Preparation of test solutions (including any steps to neutralize the antimicrobial properties of any preservatives, etc present in the sample)

Categories	Type of Tests	Specific Requirements
		<p>iii) Test for Media Sterility and Growth Promotion Test</p> <p>iv) Dilution schemes for test and standard solutions.</p> <ul style="list-style-type: none"> • Application of test & standard solutions (volume, use of latin squares, etc.) • Incubation temperature & time • Interpretation of result • Detailed calculation for the test including ANOVA table and other data showing validity of test results.
Safety tests	Pyrogen Test	<p>a. List of depyrogenated or pyrogen-free apparatus, glassware and reagents</p> <p>b. Temperature recording system</p> <p>c. Retaining conditions of the animals</p> <p>d. Selection of animals for test</p> <p>e. Preliminary test/ Sham test procedure</p> <p>f. Detailed test procedure</p> <p>g. Volume and dose of injection</p> <p>h. Interpretation of test results</p>
	Bacterial Endotoxins Test (BET) or Limulus Amebocyte Lysate (LAL) Test	<p>a. Certificate of analysis for endotoxin and LAL (limulus amebocyte lysate) reagent</p> <p>b. List of depyrogenated or pyrogen-free apparatus, glassware and reagent</p> <p>c. Preparation of standard solutions, LAL reagent/ substrate, sample</p> <p>d. Detailed calculation for determination of maximum valid dilution (MVD)</p> <p>e. The product's endotoxin limit concentration (ELC) and source of</p>

Categories	Type of Tests	Specific Requirements
		<p>information</p> <p>f. Detailed calculation for determination of endotoxin limit concentration if the ELC is not in BP, USP, JP or EP</p> <p>g. Detailed test procedure</p> <p>h. Calculation and interpretation of test result</p>
	Sterility Test	<p>a. List of media and reagent</p> <p>i) Culture media</p> <p>ii) List of rinsing solution, buffer solution and diluent</p> <p>iii) Neutralizing agent (if any)</p> <p>b. Preparation of media & Composition of Rinsing Buffer</p> <p>c. Test for Media Sterility and Growth Promotion Test</p> <p>d. Preparation of test sample (including steps to eliminate antimicrobial activity due to antibiotic samples or samples which contain preservatives).</p> <p>e. Detailed test procedure for sterility test</p> <p>i) Quantity of sample / Volume of sample</p> <p>ii) Membrane filtration / Direct inoculation</p> <p>iii) Open System or Closed System (if uses Membrane filtration method)</p> <p>iv) Volume of rinsing fluid</p>
	* Microbial Contamination Test	<p>a. Preparation of media</p> <p>b. Test for Growth Promoting, Inhibitory and Indicative Properties of Media</p> <p>c. Preparation of test sample (including neutralizing of preservatives for</p>

Categories	Type of Tests	Specific Requirements
		<p>samples that contain preservatives)</p> <p>d. Total Viable Aerobic Count</p> <ul style="list-style-type: none"> Detailed test procedure for Total Aerobic Microbial Count (TAMC) and Total Yeasts and Moulds Count (TYMC) by Plate Count, Membrane Filtration or Most-Probable Number (MPN) method. <p>e. Test for Specified Microorganisms</p> <ul style="list-style-type: none"> Detailed test procedure for each specific microorganism tested (including identification and confirmation test) Specification and acceptance criteria <p>For details, please refer circular Bil (4) dlm. BPFK/PKK/12/05</p>
	Myrocystin test	<p>For a product containing Aphanizomenonflosaquae, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method</p>

*** Note:**

Manufacturer shall ensure that products manufactured locally or overseas are free from any contamination of Burkholderia Cepacia. Please refer to these circulars for details:

[Pekeliling Ujian Burkholderia cepacia.pdf](#)

[Pekeliling Ujian Kontaminasi Burkholderia cepacia](#)

10. GUIDELINE FOR THE SUBMISSION OF ANALYTICAL METHOD VALIDATION (AMV) DOCUMENTS

10.1 TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

- a) Identification tests
- b) Quantitative tests for impurities' content
- c) Limit tests for control of impurities
- d) Quantitative tests of the active ingredient in the sample (assay and dissolution)
- e) Pyrogen or Bacterial endotoxin test
- f) Sterility test
- g) Microbial Contamination Test
- h) Biological Assay of Antibiotics

10.2 TYPICAL VALIDATION PARAMETERS FOR CHEMICAL TESTS

10.2.1 FULL VALIDATION FOR IN-HOUSE METHODS

Please refer to Table IX on next page.

TABLE IX:

Characteristics	Type of Analytical Method			
	Identification	Testing for Impurities		<u>Assay:</u> - dissolution (measurement only) - content/ potency
		Quantitation	Limit	
Accuracy		√		√
Precision		√		√
Repeatability		√		√
Interm. Precision		√ (1)		√ (1)
Specificity (2)	√	√	√	√
Detection Limit		(3)	√	
Quantitation Limit		√		
Linearity		√		√
Range		√		√

10.2.2 PARTIAL VALIDATION FOR COMPENDIAL/ PHARMACOPOEIAL METHODS

TABLE X:

Characteristics	Type of Analytical Method			
	Identification	Testing for Impurities		<u>Assay:</u> - dissolution (measurement only) - content/ potency
		Quantitation	Limit	
Precision Interm. Precision				√ (1)
Specificity (2)	√	√	√	√
Detection Limit		(3)	√	
Quantitation Limit		√		

Note:

√ signifies that this characteristic is normally evaluated.

- (1) In cases where reproducibility has been performed, intermediate precision is not needed.
- (2) Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).
- (3) May be needed in some cases.

10.3 TYPICAL VALIDATION CHARACTERISTICS FOR MICROBIOLOGICAL TESTS:

Table XI:

Microbiological tests	Validation characteristics
Bacterial Endotoxin Test	a. Test for Confirmation of Labelled Lysate Sensitivity (Verification of criteria for standard curve) b. Test for Interfering Factors (Inhibition/ Enhancement tests)
Sterility Test	Validation (Bacteriostasis or Fungistasis) Test <ul style="list-style-type: none"> Quantity of Sample/ Volume of Sample Membrane filtration/ Direct inoculation Open System or Closed System (if uses Membrane filtration method) Volume of rinsing fluid
Microbial Contamination Test	a. Validation of total viable aerobic count (suitability of the counting method in the presence of product) b. Validation of test for specified microorganism (suitability of the test method)
Microbiological Assay of Antibiotics	Linearity of the dose response relationship

Note:

1. All the analytical validation done by the industry should be in accordance to ASEAN Guidelines for Analytical Procedures, ICH Technical Requirements for Registration of Pharmaceuticals for Human Use under Validation of Analytical Procedures: Text and Methodology Q2 (R1), British Pharmacopoeia (BP) or United State Pharmacopoeia (USP).
2. The applicants should ensure all documents available in the online Quest system are of the latest versions. All correspondence on the protocol of analysis and analytical method validation should comply with any relevant circulars regarding the registration process. Failure to do so may cause cancellation or rejection of product registration

(Reference: Circular [Bil \(08\) dlm. BPFK/PPP/01/03](#))

11. GUIDELINE FOR THE SUBMISSION OF PRODUCT SAMPLES FOR LABORATORY TESTING

The submission of sample for laboratory testing is as part of the registration process. This guideline consists of the general and specific requirements for the submission of samples to the Centre for Quality Control for laboratory testing. The general requirements define the condition of the samples to be submitted whereas the specific requirements illustrate the additional details needed according to the category of product.

The applicant is given a period of **14 days** from the date of confirmed payment to send samples for laboratory testing. If the samples are not submitted within the specified time frame, the product registration application shall be tabled to the Authority for rejection.

The applicants shall comply with these requirements and failure to meet any of these requirements may cause rejection of the samples.

11.1 GENERAL REQUIREMENTS

- a) After the registration payment has been approved, applicants must make appointment with the Laboratory Services Unit for the submission of registration samples for laboratory testing.
- b) Requirements for samples:
 - i) Samples submitted must be in their original packaging & labeling.
 - ii) Samples submitted must be from the same manufacturing premise as stated in the application for registration.
 - iii) Samples submitted must have an expiry date of least one (1) year from the date of submission.
- c) For imported products, applicants are required to submit the original import permit together with the samples for laboratory testing. The import permit will be issued by the Centre for Registration and Centre for Quality Control for natural product and pharmaceutical products, respectively. The applicant should ensure that the import permit is endorsed by the enforcement officer at the entry point.
- d) The payment voucher and approved payment application status should also be submitted together with the samples.

11.2 SPECIFIC REQUIREMENTS

11.2.1 NATURAL PRODUCTS

Quantity of samples submitted must be:

- a) a minimum of 6 separate containers of all dosage forms with total contents of not less than 200 g or 200 mL; OR
- b) a minimum of 60 pieces of plasters or patches with total of not less than 200g.

11.2.2 PHARMACEUTICAL PRODUCTS

(Upon request from NPCB)

- a) An official certificate of analysis and the recent shelf-life specification from the manufacturer for the same batch of sample must be submitted with the sample.
- b) Quantity of samples submitted must be in accordance with the quantity requested.
- c) Other materials such as HPLC columns, reagents, etc must be submitted when requested.
- d) Reference standards are required to be submitted along with the pharmaceutical products. Requirements for these reference standards are as follows:
 - i) The type & quantity of reference standards submitted must be in accordance with the type & quantity requested;
 - ii) Reference standards submitted must have an expiry date of least one (1) year from the date of submission. In special situations, an expiry date of not less than six (6) months can be accepted;
 - iii) All reference standards must be accompanied by an official certificate of analysis for the same batch with the stated purity (as is, dried, anhydrous etc.) and all other relevant information (water content, loss on drying etc.);
 - iv) All reference standards must be properly labeled with name, batch number, purity and expiry date;
 - v) All reference standards must be submitted in small sealed air-tight amber glass containers.

11.3 APPEAL FOR RETESTING

- a) Applicants are allowed only one (1) appeal for any sample that fails laboratory testing (except if found to be adulterated) the Centre for Quality Control subjected to approval by the Deputy Director, Centre for Quality Control.
- b) Appeal for retesting must be submitted through the on-line registration system within 30 days from the date of result being released.
- c) If no appeal within 30 days or appeals received after 30 days or the appeal is rejected, the original test result is final and the sample will be considered as failed laboratory testing.
- d) Upon approval of appeal for retesting, an applicant needs to submit new sample, reference standards (if required), and other relevant materials (if required) as requested earlier. They should also submit the payment voucher and approval letter for the appeal. This sample shall be treated as a new registration sample and the applicant will be endured all the cost on the sample analysis.

(Reference: Circular [Bil \(67\) dlm BPFK/02/5/1.3](#))

- e) The result of the re-tested sample is final and there is no provision for a second appeal.

SECTION D: INSPECTION & LICENSING

Inspection and licensing of manufacturing premises or facilities, importers and wholesalers of registered products or notified cosmetics on the basis of compliance with Good Manufacturing Practice (GMP) as well as [Good Distribution Practice \(GDP\)](#) are vital element of drug control. Compliance to GMP is a prerequisite for the application of a manufacturing license as well as product registration or cosmetic notification whereas compliance to GDP is a prerequisite for the application of a wholesale license or import license.

12. INSPECTION

Inspection of GMP and GDP are conducted to ensure manufacturers', importers' and wholesalers' compliance towards the current GMP and GDP requirements besides ensuring the registered products and notified cosmetics that are put in the market are safe, efficacious and of quality.

The related GMP and GDP guidelines referred are as below in **Table XII**:

Guidelines	Product Type/ Category
PIC/S Guide to Good Manufacturing Practice for Medicinal Products *	Pharmaceuticals (Poison and Non-Poison) Veterinary Products
GMP Guideline for Traditional Medicines and Health Supplements, 1st Edition, 2008	Traditional Products Health Supplements
Guidelines on Good Manufacturing Practice (GMP) for Cosmetic (Annex 1, Part 9)	Cosmetics
Supplementary Guidelines on GMP for Veterinary Premixes, Supplements and Herbal/ Natural Preparations, 1 st Edition, 1 January 2012	Veterinary Products
Guidelines on Good Distribution Practice (GDP); 1st Edition 2011	For activities related to the storage and distribution by manufacturers, importers and wholesalers (where applicable)

* Refer to Pharmaceutical Inspection Co-operation Scheme (PIC/S) website at www.picscheme.org

Additional Information:

For manufacturing activity via campaign basis for carbapenem and monobactam product in area or manufacturing facility for cephalosporin product, please refer circular [\(1\)d/m.BPFK/30/06/2 Bhgn 2](#).

12.1 FOREIGN GMP INSPECTION

PRH must provide acceptable evidence to show that the manufacturer of the product follows an internationally accepted standard of Good Manufacturing Practice (GMP) and recognized by the Authority in Malaysia.

The Control of Drugs and Cosmetics Regulations 1984 (CDCR) requires that the standard of manufacture and quality control of medicinal products manufactured outside Malaysia is taken into consideration before the products are registered with the Authority. NPCB as the secretariat to the DCA is responsible to ensure all manufacturers of registered products in Malaysia are able to provide acceptable evidence that the manufacturing premises conform to current GMP requirements. Hence, foreign manufacturers are also subjected to GMP conformity assessments through acceptable GMP evidence or GMP inspection.

For details and [forms](#), please refer [Guidance Document on Foreign GMP Inspection](#).

13. LICENSING

According to the Controls of Drugs and Cosmetics Regulations 1984, any company that want to manufacture, import or wholesale any registered products need to have a valid Manufacturer's License, Import License or Wholesale License.

13.1 TYPES OF LICENSES

Table XIII:

Type of Licenses	Activity
Manufacturer's License	Licensed Premises is allowed to: Manufacture registered products and to sell by wholesale or supply their products
Import License	Licensed Premises is allowed to: Import and sell by wholesale or supply registered products
Wholesaler's License	Licensed Premises is allowed to: Sell by wholesale or supply registered products

13.2 LICENSE APPLICATION FORM

- The license application for registered products (Manufacturer's License, Import License and Wholesaler's License) shall be submitted by filling [Borang BPFK-413](#) Application for License for Registered Product.
- Application form must be submitted with the following supporting documents.
 - Company's Organization Chart
 - Location Map of Premise
 - Layout Plan of Premise
 - List of Storage Equipments
 - Details of other products (Non-medicinal) stored at the same premise
 - A copy of Business License (Local Authority) for business premise or store (if any)
 - A copy of Applicant's/License Holder's Identity Card
 - A copy of Annual Retention Certificate and/or Type A License (This document is necessary if products manufactured/ imported/ wholesale are Scheduled Poison A products or any other products that require a Pharmacist)
 - A copy of previous license (For renewal application)
- An application shall only be processed if it is complete and payment has been approved.

4. The processing fee shall not be refundable. The processing fee of an application for a Manufacturer's License is RM 1,000.00 and RM 500.00 for an [Import License](#) or a Wholesaler's License.
5. Each license is valid for **one (1) year**.

13.3 ADDITIONAL LIST OF LICENSE FOR REGISTERED PRODUCTS

1. Additional list of License are issued based on the application submitted when the products are newly registered, changing of manufacturer or importer or any registered left out products from the products list of Manufacturer's License and Import License.
2. When submitting the application form for Additional List of License for Registered Products the documents that shall be attached together are a copy of Manufacturer's License/ Import License and a copy of approval letter from the Authority (The Authority's meeting result).
3. The application of additional list shall be submitted by filling [Borang BPFFK-413T](#) Application for (Additional) Product List of License for Registered Product.

13.4 GMP CERTIFICATE

1. GMP certificates are issued for the purpose of exportation of locally manufactured registered products. It endorses that the local manufacturer complies with the current GMP requirements. These certificates are required by the overseas regulatory agencies for products registration in their countries. Thus, when filling in the GMP certificate application form, the correct address of the overseas regulatory agencies given by the company is crucial.
2. The application of GMP Certificate shall be submitted by filling [Borang BPFFK-420](#) *Permohonan Sijil Amalan Perkilangan Baik (APB)*.
3. A fee of RM50.00 is payable on the issue of such certification.

SECTION E: POST-REGISTRATION PROCESS

14. MAINTENANCE OF REGISTRATION

Registration of a product shall be valid for **five (5) years** or such period as specified in the registration certificate (unless the registration is suspended or cancelled by the Authority).

Application for renewal of product registration of a product shall be done **within six (6) months prior to the expiry** of the validity period of a product registration. After the expiry date, status of product registration shall change to status of expired, and application for renewal of the product registration can't be submitted.

In order to maintain registration of an imported product, starting on 1st January 2014, applicant shall comply with GMP requirement as stated in the **directive** issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984 *Arahan Bil. 1 Tahun 2012 Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB)* (Reference: Circulars [Bil \(25\) dlm BPFK/PPP/01/03 Jld 1](#) and [Bil \(96\) dlm.BPFK/PPP/01/03 Jld. 2](#)). The Authority shall not consider any renewal application that fails to comply with the stipulated requirement.

For pharmaceutical products which were submitted for registration before 2009, applicants shall ensure that stability study for the products at zone IV B has been conducted and granted variation approval before submission of registration renewal application. Please refer the following circulars for more information:

- a) [\(1\)dlm.BPFK/PPP/01/03Jld.3](#), 5 April 2013;
- b) [\(5\)dlm.BPFK/PPP/01/03](#), 14 August 2013.

15. WITHDRAWAL OF PRODUCT REGISTRATION

The Product Registration Holder shall inform the Authority pertaining to decision to withdraw the registration of a product before the end of the validity of such registration and shall state the reasons for the decision. The onus is on the holder to inform the manufacturer/ contract manufacturer.

The registration of a product, once withdrawn, shall not be reinstated and certificate of registration of the withdrawn product shall be invalid.

A new application shall be submitted if the product registration is required again at a later date.

16. AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

Throughout the life cycle of a registered product, changes to improve the product's efficacy, quality and safety are likely to occur. Therefore, applicant shall inform the Authority pertaining to any changes or amendment to particulars of a registered product via applications.

Starting on 1st January 2014, applicant who wishes to apply for any application for imported products of which GMP requirement shall be considered, such as change of manufacturing site and variation, shall comply with the requirement, as stated in **directive** issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984 *Arahan Bil. 1 Tahun 2012 Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB)* (Reference: Circulars [Bil \(25\) dlm BPFK/PPP/01/03 Jld 1](#) and [Bil \(96\) dlm BPFK/PPP/01/03 Jld. 2](#)). The Authority shall not consider any application in which the requirement is failed to comply with.

16.1 VARIATION

16.1.1 VARIATION APPLICATION FOR FULL EVALUATION PRODUCTS

Variation application for full evaluation products shall follow [Malaysian Variation Guideline \(MVG\)](#) as stated in the directive issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984 *Direktif untuk melaksanakan Malaysian Variation Guideline (MVG)* (Reference: [Circulars Bil \(2\) dlm BPFK/PPP/07/25.](#))

If deemed necessary, NPCB reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all categories of product.

The registration of a product shall be **reviewed for suspension or cancellation** if changes that fall under Major Variation (MaV) and Minor Variation Prior Approval (MiV-PA) are implemented without prior approval of the Authority.

For the interim period before implementation of MaV and MiV-PA according to MVG, [Appendix 12](#) is still applicable. Type I variations that are not listed under Minor Variation Notification (MiV-N) will be processed as a Type II variation.

MODE OF SUBMISSION

Table XIV:

No.	Variation	QUEST 2 Product	QUEST 3 Product
1.	Minor Variation Notification (MiV-N)	<p>Applicant shall submit application for MiV-N via both <u>manual and online</u> QUEST 2 system.</p> <p>For manual submission, applicant can download Form BPFK 416.3 from NPCB's website www.bpfk.gov.my, and shall submit to the Variation Section, Centre of Post Registration, NPCB.</p> <p>For submission online, please scan the form and attach together with the revised draft of package insert and labelling as a single file.</p>	Applicant shall submit application <u>manually</u> to the Variation Section, Centre of Post Registration, until further notice pertaining to online submission.
2.	Minor Variation Prior Approval (MiV-PA) & Major Variation (MaV)	Applicant shall submit application via <u>online</u> QUEST 2 system.	

16.1.2 VARIATION APPLICATION FOR ABRIDGED EVALUATION PRODUCTS

Variation refers to change of particulars of a registered product. No change of any particulars of a registered product shall be made without prior approval from NPCB. The registration of a product shall be **reviewed for suspension or cancellation** if changes are implemented without prior approval of the Authority.

There are two types of variation, which are Variation Type I and Variation Type II:

Table XV:

No.	Variation	
	Type I: Minor change	Type II: Major change
1.	Change in name of manufacturer and/or other manufacturers without any change in address of site	Change of product name
2.	Replacement, addition or deletion of company logo on the packaging components (without any changes on graphic or label content)	Change in content of leaflet or prescribing information/ Patient Information Leaflet (PIL)/ Summary of Product Characteristics (SPC)
3.	Change in product owner	Change in content of label inclusive of change in graphics/ artwork
4.	Change in importer/ store address	Change in manufacturing process of the finished product
5.	Change or addition of imprints, bossing or other markings (except scoring/ break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking	Change in overage of active ingredient or excipient
6.	Change in shape or dimensions of the container or closure without any other changes	Replacement of an excipient with a comparable excipient and/or change in content of excipient

No.	Variation	
	Type I: Minor change	Type II: Major change
7.	Change in pack size of the drug product (Finished product), without change in primary packaging material; or change in the number or units (e.g. tablets, ampoules) in a pack; or change in volume of non sterile preparations	Change in batch size
8.	Tightening of specification limits of drug product (finished product) and/or drug substance (active ingredient)	Change in hard capsule shell (color, size or source)
9.	Change in particular of manufacturer of drug substance (active ingredient) without any change in specification: <ul style="list-style-type: none"> - Change in manufacturer of drug substance - Addition of manufacturer of drug substance - Change in name and/or rephrasing of address of a manufacturer of drug substance 	Change in finished product or active ingredient specification (includes addition of a new test parameter)
10.	Change in secondary packaging material (or change in any part of the primary packaging material that is not in contact with the finished product (e.g. color of flip off caps, color code rings on ampoules, change of needle shields i.e. different plastic used)	Change to in-process tests or limits applied during manufacture of the product
11.	Change in testing procedure of an excipient.	Change or addition in primary packaging material

No.	Variation	
	Type I: Minor change	Type II: Major change
12.		Change in shelf life of finished product: <ul style="list-style-type: none"> - As packaged for sale - After first opening - After dilution/ reconstitution
13.		Change in storage conditions
14.		Appointment, deletion or change of other manufacturers
15.		Addition or deletion of scoring/ break line on tablet
16.		Change in test procedure or analytical protocols of finished product
17.		Change or addition of fill volume and/or change of shape or dimension of container or closure for a sterile solid and liquid drug product

All supporting documents in accordance to the specified conditions laid down for each type of variations should be submitted. For further information pertaining to conditions and supporting documents required for an application of variation, please refer to [Appendix 12: Conditions and Supporting Documents Required for Application of Variation Type I & Type II](#).

If deemed necessary, NPCB reserves the right to request for additional supporting documents and variation approval letters from other regulatory bodies for all categories of product.

The applicant shall provide to NPCB the reason for variation applied. For every variation being made, reason for variation/ remarks, should be clearly written and explained. Other supporting documents can be attached at F12 where such documents are necessary.

MODE OF SUBMISSION

Table XVI:

No.	Variation	QUEST 2 Product	QUEST 3 Product
1.	Type I	<p>Applicant shall submit application for Variation Type I via both <u>manual and online</u> QUEST 2 system.</p> <p>For manual submission, applicant can download Form BPFK 416.2 from NPCB's website www.bpfk.gov.my, and shall submit to the Variation Section, Centre of Post Registration, NPCB.</p>	<p>Applicant shall submit application for Variation Type I and/or Type II <u>manually</u> to the Variation Section, Centre of Post Registration, until further notice pertaining to online submission.</p>
2.	Type II	<p>Applicant shall submit application for Variation Type II via <u>online</u> QUEST 2 system.</p>	

16.1.3 OTHER INFORMATION

- a) In the event that a variation application is complex, consultation with relevant officer is encouraged, prior to submission of the application into the online QUEST 2 system.
- b) The online QUEST 2 variation module is an overwrite-system. For data already approved in the system which is intended to be retained, it shall be submitted together under “proposed change data”. For instance, whereby existing approved packaging is “HDPE bottle” while the proposed variation is to include “blister pack”, stability data for both packaging (combined into a single file) is required to be submitted during application for variation.
- c) No correspondence with the applicant for Quest 2 variation module can be made. For any rejection made for a certain field, only the main field will be rejected (i.e. the supportive documents will be kept until the main field is resubmitted). However, if the main field is not resubmitted without any reason for a certain period of time, the supportive documents will be rejected and a new application shall be submitted.

16.2 CHANGE OF MANUFACTURING SITE

Change of Manufacturing Site (COS) refers to change of manufacturing site for certain part or all of the manufacturing process of a product, but it does not cover changes related to a new site, where only:

- a) batch release takes place OR
- b) to a new packager (secondary packaging or labelling), as these changes are covered under applications for amendments to the particulars of a registered product (variation). Please refer to paragraph [Section E: 16.1 Variation](#).

However, a change of manufacturing site for biologics shall require a new product application only if the change is extensive that will have an impact on the quality, safety and efficacy profile of the final product.

Upon receipt of complete application, the application shall be processed within forty-five (45) working days.

16.2.1 CONDITIONS ON APPLICATION FOR COS:

Change in Manufacturing Site is only applicable in the following situations:

- a) a change in manufacturing site for the same company, including rationalization in the event of mergers; and
- b) a company which previously contracts out the manufacture of its product(s), transfers the manufacture of the product to its own premises.

A change in manufacturing site between contract manufacturers is not routinely allowed but may be considered in a crisis situation (refer Type V COS: Crisis Situation)

Validity of registration for a product which has been approved for change of manufacturing site remains unchanged, without any extension of the validity.

16.2.2 CONDITIONS ON GOOD MANUFACTURING PRACTICE (GMP):

- a) The new manufacturing site shall comply with current Good Manufacturing Practice (cGMP);
- b) Local manufacturing sites are subjected to pre-licensing inspections by the NPCB inspectors;

- c) For manufacturing sites outside Malaysia, certification on GMP by the competent authority is acceptable.
- d) The Authority reserves the right to conduct an inspection on any manufacturing site.
- e) For further information pertaining to the requirements on GMP, please refer to these circulars and directive.
 - i) [Bil \(35\) dlm. BPFK/PPP/01/03](#)
 - ii) [Bil \(40\) dlm. BPFK/PPP/01/03](#)
 - iii) [Bil \(25\) dlm BPFK/PPP/01/03 Jld 1](#)
 - iv) [Bil \(96\)dlm.BPFK/PPP/01/03 Jld. 2](#)

16.2.3 TYPES OF MANUFACTURING SITE CHANGES (COS)

Table XVII:

No.	Types of COS		Description
1.	Type I	Change of manufacturing site within Malaysia	Change in the location of the site of manufacture within Malaysia only. This change may be due to upgrading of facilities, and/or expansion of manufacturing activities or moving to a newly constructed plant.
2.	Type II	Change of manufacturing site from foreign country to Malaysia	Change in location of the site of manufacture from outside of Malaysia to a location in Malaysia. This change may be due to the ability of the local counterpart to manufacture the product.
3.	Type III	Change of manufacturing site located outside Malaysia	Change of location of the site of manufacture to manufacturing facilities located outside Malaysia. This may be due to a merger or rationalization of manufacturing sites in line with multinationals' manufacturing strategies.

No.	Types of COS	Description
4.	Type IV Change of manufacturing site for sterile products	<p>i) Transfer of manufacturing of an aseptically processed sterile product to a:</p> <p>a) newly constructed or refurbished aseptic processing facility or area;</p> <p>b) an existing processing facility or area that does not manufacture similar approved products. (For example, transferring the manufacture of a lyophilized product to an existing aseptic process area where there is no approved lyophilized product is manufactured).</p> <p>ii) Transfer of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site.</p> <p>Once this change has been approved, subsequent site changes to the facility for similar types of product and processes will not be categorized as a Type IV COS.</p>
5.	Type V Change of manufacturing site in crisis situation	<p>i) Change of location of the site of manufacture that is deemed necessary due to certain circumstances such as natural disasters, closure or suspension of premise (revocation of manufacturing license) and matters related to breach of product quality, safety and efficacy ONLY.</p> <p>ii) Prior to submission of Type V COS, approval letter issued by the secretariat of the Authority shall be obtained.</p> <p>iii) Application for Type V COS must be made within three (3) months from the date of the crisis.</p>

16.2.4 MODE OF SUBMISSION

- a) Complete application for COS with supporting documents shall be submitted manually to Variation Section, Centre of Post-Registration, NPCB.
- b) For submission of COS Type II to Type V, applicant can download [Form BPFK 415.3](#) from NPCB's website www.bpfk.gov.my under Industry - Forms. Submission of completed application form with supporting documents shall be made together with processing fees, according to category of product, as stipulated in the form.

16.2.5 OTHER INFORMATION

- a) Application for COS will be rejected if applicant failed to submit required data within **six (6) months** from the first correspondence date;
- b) All supporting documents in accordance to the specified conditions laid down for each type of COS should be submitted. For details, please refer to [Appendix 13: Supporting Documents Required for Change of Manufacturing Site Application](#).
- c) If deemed necessary, NPCB reserves the right to request for additional supporting documents.
- d) For further information pertaining to COS, please refer these circulars.
 - i) [Bil \(59\) BPFK/17/VF/9.2](#)
 - ii) [Bil \(22\) dlm. BPFK/PPP/01/03](#)
 - iii) [Bil \(31\) dlm. BPFK/PPP/01/03](#)
 - iv) [Bil \(39\) dlm. BPFK/PPP/01/03](#)
 - v) [Bil \(10\) dlm BPFK/PPP/01/03 Jld 1](#)

16.3 CHANGE OF PRODUCT REGISTRATION HOLDER

[Reference: [Directive \(3\)dIm.BPFK/PPP/07/25](#)]

16.3.1 INTRODUCTION

A transfer procedure shall be used where a product registration for the purpose of marketing authorization to be transferred from the existing product registration holder (PRH) to another holder. This procedure allows the same product to maintain the same registration number.

Upon receipt of complete application, the application shall be processed within forty-five (45) working days.

16.3.2 CONDITIONS

The conditions for the PRH transfer procedure are as follows:

- 1) An application to transfer the marketing authorization of a product shall be submitted by the **existing PRH**.
- 2) The new PRH shall be a registered company/ business with Companies Commissioner of Malaysia and a registered QUEST user with National Pharmaceutical Control Bureau (NPCB).
- 3) The existing product registration shall have a remaining validity **period of at least six (6) months**. If the period is less than six (6) months, product registration renewal shall be made before the transfer application is submitted.
- 4) No change/s can be made to the technical data or approved pharmaceutical / pharmacological information, including the texts of the product label and leaflet, **except** the name and address of the approved PRH, unless made through variation procedure.
- 5) In the interim, the existing PRH is still vested with the marketing authorization of the said registered product.
- 6) The transfer shall come into effect on the day the DCA makes its decision on the application. Upon the transfer of product registration to the new PRH, the authorization issued to the previous PRH will be cancelled as the product cannot be marketed simultaneously by two different PRHs. The new PRH shall bear responsibility for the said product.

- 7) However, the existing PRH is allowed to deplete the stocks and still holds the responsibility in the event of pharmacovigilance issues or quality defects associated with the product arises during the interim transfer period.
- 8) The existing PRH or new approved PRH shall submit a written request to deplete existing stocks after DCA approval for the transfer. The PRH who submitted the request shall hold the responsibility in the event of pharmacovigilance issues or quality defects associated with the product.
- 9) Application shall be rejected if the applicant fails to provide satisfactory required documents within 30 working days starting from the first correspondence date.

16.3.3 APPLICATION

The existing PRH shall submit the following documents and payment to NPCB:

1. Application Form [BPFK-430.5](#)
2. *Borang Penyerahan Permohonan* [BPFK-001](#)
3. Processing Fee (refer 16.3.4)
4. Original Supporting Documents (refer 16.3.5)

16.3.4 PROCESSING FEE

1. NON-REFUNDABLE processing fee.
 - For Traditional Product : RM 500.00
 - For Poison/ Non-Poison product : RM 1,000.00
2. The processing fee shall be paid in the form of a bank draft/ money order/ postal order, made payable to "Biro Pengawalan Farmaseutikal Kebangsaan".
3. Application/s without correct processing fee will not be accepted for processing. Foreign currencies are not acceptable.

16.3.5 SUPPORTING DOCUMENTS

1. All supporting documents shall be produced in ORIGINAL copies as listed below:

LIST OF REQUIRED SUPPORTING DOCUMENTS:

- i) Letter of Authorisation (LOA) issued by overseas product owner **certified by Notary Public from the country of origin of the product owner; or Malaysia Commissioner for Oath for local product owner** and **shall consists** of the following information:
 - a. The registered name and registration number of the product(s) concerned.
 - b. Company name, business registration number and address of the proposed new PRH.
 - c. Company name, business registration number and address of the existing PRH.
 - d. Effective date of the appointment and termination given by the product owner. If the effective date is not mentioned, the date of the LOA issued will be considered as the effective date.
 - e. Signature of the Managing Director/ Director/ President/ Chief Executive Officer/ General Manager who has overall responsibility for the company or organization.
 - f. Full and complete address, email address (if available), telephone and fax number (if available) of the Product Owner.
- *Note: LOA format example (Please refer 16.3.6 Supporting Document Format Example)*
- ii) Resolution by Company Board of Directors of **local product owner** to verify that ALL Board of Directors/ Partners have given their consent to the Change of PRH.
- iii) Certified by Commissioner for Oath of the latest document indicating details of director/s and shareholder/s of **local product owner**; e.g. Form 24 and Form 49.
- iv) Resolution by Company Board of Directors of **existing PRH** to verify that ALL Board of Directors/ Partners have given their consent to the Change of PRH.
- v) Certified by Commissioner for Oath of the latest document indicating details of director/s and shareholder/s of **existing PRH**; e.g. Form 24 and Form 49.
- vi) A certified true copy of the Company/ Business Registration Certificate of proposed new PRH; e.g. Form 9 and/ or Form 13.

- vii) Statement of Acceptance as Product Registration Holder, [BPFK-430.5\(3\)](#) to be completed by proposed new PRH.
2. Date of the documents must be recent, i.e. not exceeding six (6) months from the date of application.
 3. Each page of attachment of product list (if any) must be endorsed by the signatory.
 4. The Secretariat, if necessary, has the right to request for further supplementary information or documentation. Failure to do so may result in the rejection of the transfer application.

16.3.6 SUPPORTING DOCUMENT FORMAT EXAMPLE

This format example is suggested for the applicant in order to produce the required supporting document i.e. Letter of Authorisation (LOA).

PRODUCT OWNER Letter Head (full and complete address, email address, telephone and fax number)

(Please state) Date of LOA (the existing PRH shall submit an application within 6 months from this date)

Drug Control Authority,
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor, Malaysia.

Dear Sir/ Madam,

LETTER OF AUTHORIZATION FOR TRANSFER OF PRODUCT REGISTRATION HOLDER

The above subject matter is referred.

Due to (please state) reason of the transfer,

2. We, Name of registered Product Owner, the undersigned as the product owner for the said product(s) listed below:

<u>Name of Product(s)</u>	<u>Registration Number</u>
<i>(If number of product > 10, endorsed attachment is allowed.)</i>	

hereby authorize

Company name with business registration number and full address of the proposed new PRH

to be the Product Registration Holder and to act on our behalf/ responsible for all matters pertaining to the registration of the listed product(s) including obtaining approval for any subsequent product variation and maintenance of the product(s) registration.

3. Therefore, we hereby terminate marketing authorization of the existing Product Registration Holder Company name with business registration number and full address of the existing PRH for the listed product(s) effectively on date of authorization / termination.

4. We shall confirm that the entire dossier of the listed product(s) includes all the data in support of the original application, together with all correspondence with the Drug Control Authority (DCA)/ National Pharmaceutical Control Bureau concerning the listed product(s), to be transferred from Company name of the existing PRH to Company name of the proposed new PRH upon the approval from DCA.

Thank you.

Sincerely,

*Company officer's signature(s)

*Full name & Title/ Position

Company stamp

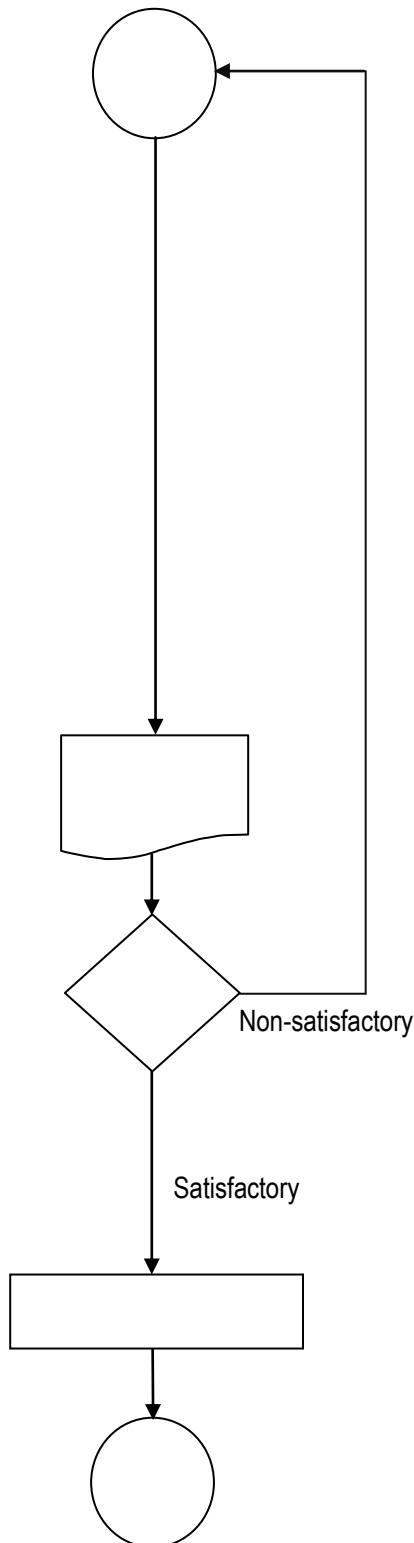
**Certified by
Notary Public/
Commissioner
for Oath

cc: Company of proposed new PRH } (A copy of LOA shall be sent to
Company of existing PRH } these companies by the
Product Manufacturer } Product Owner)

IMPORTANT NOTICE:

1. *LOA shall be signed by Managing Director/ Director/ President/ Chief Executive Officer/ General Manager who has overall responsibility for the company or organization.
2. **LOA shall be certified by Notary Public of the country of origin for overseas company or Malaysia Commissioner for Oath for local company.

16.3.7 FLOWCHART FOR THE CHANGE OF PRODUCT REGISTRATION HOLDER



Company (Existing PRH)

Submit completed application to NPCB as below;

1. Application Form BPFK-430.5
2. *Borang Penyerahan Permohonan* BPFK-001
3. Processing Fee
4. Original Supporting Documents consisting of;
 - LOA from product owner certified by Notary Public for overseas company or Commissioner For Oath for local company
 - Resolution by Company Board of Directors of local product owner
 - The latest Form 24 and Form 49 of local product owner certified by Commissioner for Oath
 - Resolution by Company Board of Directors of existing PRH
 - The latest Form 24 and Form 49 of existing PRH certified by Commissioner for Oath
 - Company/ Business Registration Certificate of proposed new PRH
 - Statement of Acceptance As Product Registration Holder; BPFK-430.5(3) completed by proposed new PRH

Secretariat

Receive documentations and evaluation of application

Secretariat

Processing of evaluated application

1. Satisfactory:
 - a) Table to DCA meeting for approval
2. Non-satisfactory:
 - b) Table to DCA meeting for rejection (processing fee is NON REFUNDABLE in the event that application is being rejected)

DCA Meeting

Secretariat

Processing of DCA meeting outcome

1. Notification of transfer approval to new proposed PRH and termination notification to existing PRH for approved application; OR
2. Notification of transfer rejection to existing PRH for rejected application

16.4 NEW/ ADDITIONAL INDICATION

New/ additional indication is defined as an indication which is not initially approved for a registered pharmaceutical product. This shall include new therapeutic indication or indication for new age group, such as usage in children, and shall not include changing/ rephrasing of sentences.

There are two (2) types of evaluation process available for a [new/ additional indication application](#):

16.4.1 FULL EVALUATION PROCESS

For new indication which has been registered in any one of the Authority's eight (8) reference countries (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan and Switzerland).

This application will require specialists' comments.

16.4.2 VERIFICATION PROCESS

For new indication which has been registered by any two reference country's authorities (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan, Switzerland and EMA).

Note:

The approved new indication in these countries should be the same as that of the proposed new indication.

Other supporting documents that are deemed necessary shall be submitted upon request to support the efficacy and safety of the proposed additional indication.

The supporting documents may include but not limited to the following:

- a) Approval of Additional Indication(s) in country of origin;
- b) Approval status in reference countries, its corresponding approval letter and approved Package Insert;
- c) Approval Indication status in ASEAN Member States and its approved corresponding package insert;

- d) Revised Package Insert;
- e) World Wide Approval status;
- f) Patient Information Leaflet (PIL);
- g) Clinical Expert Reports;
- h) Synopsis of Individual Studies;
- i) Clinical Studies Report/ In-House Clinical Trials;
- j) Published Clinical Papers;
- k) Current Periodic Safety Update Report (PSUR).

16.5 APPLICATION FOR A CONVENIENT PACK

- a) This type of application is referring to registered products which are packed together in a single packaging unit for convenience of the consumers, such as a Confinement Set or *Set Jamu Bersalin*.
- b) Individual registered products are allowed to be packed together and marketed as a convenient pack, provided that the application is justified satisfactorily.
- c) Shall consist of registered products from the category of natural product and/or health supplement only.
- d) Application for a convenient pack shall be made via the process of variation Type II.

The holder has to submit the convenient pack label and also the individual label via application for variation under Part D2 (outer label). The convenient pack label shall contain the same information as in the primary label.

For details of variation, please refer to [Section E: 16.1 Variation](#).

- e) Individual registered products involved in the convenient pack can be sold individually or as a pack.
- f) Conditions for application:
 - i) Individual registered products proposed to be packed together as a convenient pack shall be sourced from the same product owner/ PRH;
 - ii) Submission of the application shall be made by the same PRH.

- iii) The manufacturing site for the convenient pack shall be a GMP certified facility.
- g) Approved indication of each individual registered product in the convenient pack remains unchanged. There is no common specific indication for the convenient pack.
- h) Labelling requirement specifically for convenient pack:

Table XVIII:

Outer Label	Immediate Label
Contents in the labelling of each individual registered product have to be included in the outer label of the convenient pack.	As per labelling requirements for registered products.

Note:

For the purpose of application submission, if the individual registered product is also marketed independently, outer label of the packaging sold independently and outer label of the convenient pack shall be submitted together.

- i) Additional information on differentiation from Combination Pack (Combo Pack):

Table XIX:

No.	Particulars	Convenient Pack	Combination Pack (Combo Pack)
1.	New registration number (MAL No.) to be assigned upon approval	No	Yes
2.	Mode of application	Variation Type II	Application for registration as a new product
3.	Purpose of product	For convenience of the consumer	For therapeutic regimen

No.	Particulars	Convenient Pack	Combination Pack (Combo Pack)
4.	New indication	No	Yes
5.	Sale of product	Can be sold individually or as a pack	Only to be sold as a pack
6.	Example	Confinement Set or <i>Set Jamu Bersalin</i>	Klacid HP7 (for treatment of peptic ulcer diseases associated with H. pylori infection)

17. POST-MARKETING ACTIVITIES

17.1 PHARMACOVIGILANCE

17.1.1 ADVERSE DRUG REACTION REPORTING AND SAFETY UPDATES

In accordance with Regulation 28 : Reporting adverse reaction under Control of Drugs and Cosmetics Regulations 1984, Sale of Drugs Act 1952 (amendment 2006), the product registration holders or any person who possesses any registered product shall inform immediately the Director of Pharmaceutical Services of any adverse reaction arising from the use of the registered product.

All product registration holders must ensure that a pharmacovigilance system is in place by the company and appropriate action is taken, when necessary.

Product registration holders are required to monitor and report any product safety issues that arises locally or internationally to the NPCB and comply with all safety-related directives issued by the Authority.

The product registration may be cancelled if the product registration holder fails to inform the Authority of any serious adverse reactions upon receipt of such reports.

The WHO encourages reporting of ALL adverse drug reactions.

For further information, please refer [Malaysian Guidelines for the Reporting & Monitoring](#).

17.2 POST-MARKET SURVEILLANCE

- a) It is the prime responsibility of the holder to ensure products marketed are in accordance to the standards and requirements of the Authority;
- b) Registered products may be sampled and tested for compliance with official or pharmacopoeia standards or specifications agreed by the manufacturer. Labels and package inserts of the samples will also be checked to ensure compliance to the requirements as approved.
- c) The Authority will take necessary action on products which do not conform to the standards/ specifications and requirements in the form of warnings or recalls. The product registration holder has up to thirty (30) days to identify the cause of defect and actions to be taken for improvement.

17.2.1 PRODUCT COMPLAINTS

- a) The product registration holder should notify the NPCB of any product quality related problems (with registered products) that the holder is aware of;
- b) It is also the responsibility of the prescribers, pharmacists, as well as all other health professionals who come into contact with the drug to report to NPCB by using the NPCB complaint form i.e. [BPFK 419](#) / [BPFK 418.4](#) together with complaint sample (if any).
- c) All complaints received will be investigated by the NPCB as well as product registration holder/ manufacturer. It is the responsibility of the company to determine the appropriate corrective and preventive action.

[Guidelines on Good Distribution Practice, Chapter 9.](#)

17.2.2 PRODUCT RECALLS

- a) The decision for recall of a product shall be made when there is or may cause potential risk to the user of the products. Recalls may be done voluntarily by the product registration holder or as directed by the Director of Pharmaceutical Services Division, Ministry of Health Malaysia;
- b) The product registration holder is responsible for conducting recalls of defective or unsafe products. No recall should take place without first consulting/ informing the Authority.

[Guidelines on Good Distribution Practice, Chapter 10.](#)

17.3 PUNITIVE ACTION FROM THE AUTHORITY

17.3.1 ADULTERATION

As stated in circular [Bil \(30\) BPFK/PPP/01/03](#), 13th May 2009, punitive action shall be taken against companies who are involved in adulteration.

Any registered products found to have been adulterated, the following action shall be taken by the Director of Pharmaceutical Services:

- a) The registration of the related product shall be cancelled and recall of all batches of the product shall be done immediately;
- b) The manufacturer's license of the related manufacturer shall be revoked for six (6) months for the first offence and one (1) year for the subsequent offence, from the date of revocation letter;
- c) All transactions (including application for product registration, application for change of product registration holder, application for change of manufacturing site) for the adulterated product registration holder shall be frozen for six (6) months for the first offence and one (1) year for the subsequent offence, from the date of cancellation letter from the Authority.

APPENDICES

Appendix 1	Fees
Appendix 2	Requirements for Product Registration
Appendix 3	Guidelines on Registration of Biologics
Appendix 4	Guideline on Registration of Health Supplements
Appendix 5	Guideline on Registration of Natural Products
Appendix 6	Guideline on Regulatory Control of Active Pharmaceutical Ingredients (API)
Appendix 7	Special Conditions for Registration for a Particular Product or Group of Products
Appendix 8	List of Permitted, Prohibited and Restricted Substances
Appendix 9	Labelling Requirements
Appendix 10	Guideline on Patient Dispensing Pack for Pharmaceutical Products in Malaysia
Appendix 11	Guideline on Filling the Online Application Form for Product Registration via Quest System
Appendix 12	Conditions and Supporting Documents Required for Application of Variation Type I & Type II
Appendix 13	Supporting Documents Required for Change of Manufacturing Site (COS) Application

APPENDIX 1:

FEES

Outline:

- 1.1 Charges for USB Token of QUEST Membership;
- 1.2 Processing and Analysis Fee for Product Registration;
- 1.3 Charges for Application of Licence;
- 1.4 Charges for Amendments to Particulars of a Registered Product; and
- 1.5 Fee for Certificates.

1.1 CHARGES FOR USB TOKEN OF QUEST MEMBERSHIP

Application category	Charges
First-time User	Package A (USB Token of 2-years validity + Guide Manual) : COST RM335 Package B (USB Token of 1-year validity + Guide Manual) : COST RM320
Supplementary User	Package A (USB Token of 2-years validity + Guide Manual) : COST RM335 Package B (USB Token of 1-year validity + Guide Manual) : COST RM320
Renewal of USB token	Package C1 (New USB Token of 2-years validity) : COST RM280 Package C2 (Utilized old USB Token of 2-years validity) : COST RM100

1.2 PROCESSING AND ANALYSIS FEE FOR PRODUCT REGISTRATION

Every application for registration shall be accompanied with a processing and analysis fee, as specified below (effective 1st January 2007):

No.	Category of Product	* Processing Fees	Analysis Fees	Total Fees
1.	Pharmaceutical	RM 1,000.00	Single active ingredient : RM 3,000.00	RM 4,000.00
	a) New Drug Products b) Biologics		Two or more active ingredients : RM 4,000.00	RM 5,000.00
2.	Pharmaceutical	RM 1,000.00	Single active ingredient : RM 1,200.00	RM 2,200.00
	a) Generic (Scheduled Poison) b) Generic (Non-Scheduled Poison) c) Health supplement		Two or more active ingredients: RM 2,000.00	RM 3,000.00
3.	Natural Product	RM 500.00	RM 700.00	RM 1,200.00

* As stipulated in the CDCR 1984, Regulation 8.

1.3 CHARGES FOR APPLICATION OF LICENSES

After a product is registered, the applicant shall apply for a manufacturer/ import/ wholesale license. The processing fees are as specified below:

License	Processing fee	Timeline	Validity
1. Manufacturer	RM 1,000.00	Not more than 1 month	1 year
2. Import	RM 500.00	Not more than 1 month	1 year
3. Wholesale	RM 500.00	Not more than 1 month	1 year

1.4 CHARGES FOR AMENDMENTS TO PARTICULARS OF A REGISTERED PRODUCT

Types of Amendment	Processing fee	
	Pharmaceutical	Natural Product
1. Change of Manufacturing Site (Type II, III, IV, V)	RM 1,000.00	RM 500.00
2. Change of Product Registration Holder	RM 1,000.00	RM 500.00

1.5 **FEE FOR CERTIFICATES**

Under the CDCR 1984, Regulation 16: *“The Director of Pharmaceutical Services may issue such certification on any matter relating to any product where such certification is required by any country importing such a product.”*

Certificates	Fee	Validity
Issuance of one (1) Certificate of Pharmaceutical Product	RM 50.00	2 years
Issuance of one (1) Certificate of Good Manufacturing Practice (GMP)	RM 50.00	2 years

APPENDIX 2:

REQUIREMENTS FOR PRODUCT REGISTRATION

IMPORTANT NOTES:

1. This appendix is for reference purpose only, where applicable, and it may not follow the sequence as in the online product registration application forms (in QUEST system).
2. Online application forms are available for different product categories.
3. Applicant shall follow and comply with all requirements in the online application forms as well as any supplementary documentation requested by the Authority, whichever it may deems fit.

This appendix comprises of two (2) parts which are:

2.1 General requirements for:

2.1.1 Full Evaluation;

(In accordance to ASEAN ACTD/ ACTR or ICH guidelines)

- Part I Administrative data and product information
- Part II Data to support product quality (Quality Document)
- Part III Data to support product safety (Nonclinical Document)
- Part IV Data to support product safety and efficacy (Clinical Document)

2.1.2 Abridged Evaluation.

2.1.3 Additional Information on Requirement of:

- Bioavailability (BA) Study
- Bioequivalent (BE) Study

2.2 Product Specific Requirements

2.1 GENERAL REQUIREMENTS

Data to be submitted as general requirement to support an application for product registration is based on the product category as shown below:

(A) FULL EVALUATION (based on ACTD/ ACTR)					
No.	Product Category	Part I	Part II	Part III	Part IV
1.	New Drug Products	√	√	√	√
2.	Biologics	√	√	√	√
3.	Generics (Scheduled Poison)	√	√	Not Applicable	Not Applicable
4.	Generics (Non-Scheduled Poison)	√	√	Not Applicable	Not Applicable
5.	Health Supplements: Disease Risk Reduction Claims (High)	√	√	√	√
(B) ABRIDGED EVALUATION					
No.	Product Category				
1.	* Generics (Non-Scheduled Poison)				
2.	Health Supplements: a) General or Nutritional Claims b) Functional Claims (Medium)				
3.	Natural Products				

* Generics (non-scheduled poison) which are evaluated under abridged evaluation include, but not limited, to the following:

- a) Antiseptics/ skin disinfectants;

- b) Locally-acting lozenges/ pastilles;
- c) Topical analgesic/ counter-irritants;
- d) Topical nasal decongestants;
- e) Emollient/ demulcent/ skin protectants;
- f) Keratolytics;
- g) Anti-dandruff;
- h) Oral care;
- i) Anti-acne;
- j) Medicated plasters/ patch/ pad; and
- k) Topical antibacterial.

2.1.1 GENERAL REQUIREMENTS FOR FULL EVALUATION

No.	Step I: Product Validation
1.	Is your product has a brand name? (Yes/ No) (If yes, please provide brand name and product name)
2.	Dosage Form
3.	Active Ingredient(s) a) Active Ingredient Name b) Strength of Active Ingredient (Quantity unit/ dose) c) Source of Active Ingredient (Animal – e.g. Bovine, Porcine, Ovine or Others/ Plant/ Others) d) Form of Active Ingredient e) Remarks (if any)
4.	Excipient(s) a) Excipient name b) Strength of Excipient (Quantity unit/ dose) c) Function of excipient (e.g. absorbent, diluents, bulking agent, coating agent, anti-caking agent etc.) d) Source of excipient e) Remarks (if any)
5.	Is there any source of ingredients derived from animal origin, including active ingredient? (Yes/ No)
6.	Manufacturer (Name and Address)
7.	Is the selected manufacturer a contract manufacturer? (Yes/ No)
8.	Is the product from second source? (Yes/ No) If yes, please provide: a) Letter of declaration stating that this product is a second source product b) Registration number and product name of the first source
9.	Is this product containing any premix? (Yes/ No) a) State your premix form b) Manufacturer name c) Manufacturer address d) Certificate of Good Manufacturing Practice (GMP) e) Formulation f) Manufacturing Process g) Specification of Analysis h) Certificate of Analysis (CoA)

No.	Step I: Product Validation
10.	Is this a replacement product? (Yes/ No) If yes, please provide: a) Letter of Declaration stating that this product is a replacement product b) Registration number and product name of the replaced product
11.	Is there any other manufacturer (repacker)? (Yes/ No) a) Manufacturer (repacker) name b) Manufacturer (repacker) address c) Certificate of Good Manufacturing Practice (GMP) d) Packaging Process
12.	Is this an imported product? (Yes/ No)

Step II:	
Part I: Administrative Data And Product Information	
No.	Section A: Product Particulars
1.	Product Name
2.	Name & Strength of Active Substance and Excipient
3.	Dosage Form
4.	Product Description
5.	Pharmacodynamics
6.	Pharmacokinetics
7.	Indication
8.	Recommended Dose
9.	Route of Administration
10.	Contraindication
11.	Warning and Precautions
12.	Interaction of Other Medicaments
13.	Pregnancy and Lactation
14.	Side Effects
15.	Symptoms and Treatment of Overdose

Step II:	
16.	Storage Condition
17.	Shelf Life
18.	Therapeutic Code/ ATC Code
No.	Section B: Product Formula
1.	Batch Manufacturing Formula
2.	Attachment of Batch Manufacturing Formula Documentation
No.	Section C: Particulars of Packing - Please refer Appendix 10 : Guide for Implementation of Patient Dispensing Pack for Pharmaceutical Products in Malaysia
1.	Pack Size (Fill details by weight/ volume/ quantity)
2.	Immediate Container Type (Container Type and Description) e.g. Aluminium/ Glass/ Metal/ Paper/ Plastic/ Others
3.	Barcode/ Serial No. (Optional)
4.	Recommended Distributor's Price (RM) (Optional)
5.	Recommended Retail's Price (RM) (Optional)
No.	Section D: Label (Mock-up) For Immediate Container, Outer Carton, Proposed Package Insert - Please refer Appendix 9 : Labelling Requirements
1.	Proposed Label Mock-up for Immediate Container
2.	Proposed Label Mock-up for Outer Carton
3.	Proposed Package Insert
No.	Section E: Supplementary Documentation
1.	Product Owner
2.	Letter of Authorization from Product Owner
3.	Letter of Appointment of Contract Manufacturer from Product Owner (if applicable)

Step II:	
4.	Letter of Acceptance from Contract Manufacturer (if applicable)
5.	Is the active ingredient(s) patented in Malaysia? (Yes/ No) (If yes, please attach the related document)
6.	Certificate of Pharmaceutical Product (CPP)
7.	CPP Issuing Body
8.	Is this product licensed to be placed on the market for use in the exporting country? (Yes/ No) (If no, please state the reason)
9.	Is the product on the market in the exporting country? (Yes/ No) (If no, please state the reason)
10.	Date of Issue of CPP
11.	Date of Expiry of CPP
12.	Certificate of Free Sale (CFS)
13.	CFS Issuing Body
14.	Date of Issue of CFS
15.	Date of Expiry of CFS
16.	Certificate of Good Manufacturing Practice (GMP)
17.	Certificate of GMP Issuing Body
18.	Date of Issue of Certificate of GMP
19.	Date of Expiry of Certificate of GMP
20.	Summary of Product Characteristics (Product Data Sheet)
21.	Patient Information Leaflet (PIL)
22.	*Attachment of Protocol Analysis
23.	*Attachment of Analytical Validation
24.	*Certificate of Analysis (CoA)
25.	Other Supporting Document (if any)
26.	Manufacturer (Name and address)

Step II:	
27.	Importer (if any)
28.	Other manufacturer(s) involved, e.g. repacker (if any) (Please attach Certificate of GMP, if yes)
29.	Store Address
PART II: QUALITY OF PRODUCT	
No.	Section P: Drug Product (Finished Product)
1.	Description and Composition
2.	Pharmaceutical Development
	a) Information on Development Studies
	b) Components of the Drug Product
	c) Finished Products
	d) Manufacturing Process Development
	e) Container Closure System
	f) Microbiological Attributes
	g) Compatibility
3.	Manufacturer
	a) Batch Manufacturing Formula
	b) Manufacturing Process and Process Controls
	c) Manufacturing Process Flowchart
	d) Control of Critical Steps & Intermediates
	e) Process Validation and/or Evaluation
4.	Control of Excipients
	a) Specifications
	b) Analytical Procedures
	c) Validation of Analytical Procedures
	d) Justification of Specifications
	e) Excipient of Human or Animal Origin

Step II:	
	f) Novel Excipients
5.	Control of Finished Products
	a) Specifications
	b) Analytical Procedures
	c) Validation of Analytical Procedures
	d) Batch Analyses
	e) Characterization of impurities
	f) Justification of Specifications
6.	Reference Standards or Materials
7.	Container Closure System
8.	Stability
9.	Product Interchangeability/ Equivalent Evidence (Bioavailability/ Bioequivalence, BA/BE) - Please refer 2.1.3 Additional information on requirements of BA and BE.
No.	Section S: Drug Substance
1.	General Information
	a) Nomenclature
	b) Structure and Attachment for Structure of Drug Substance
	c) General Properties
2.	Manufacturer
	a) Manufacturer Name and Address
	b) Description of Manufacturing Process and Process Controls
	c) Controls of Materials
	d) Controls of Critical Steps and Intermediates
	e) Process Validation and/or Evaluation
	f) Manufacturing Process Development

Step II:	
3.	Characterisation
	a) Elucidation of Structure and Characteristics
	b) Impurities
4.	Control of Drug Substances
	a) Specifications
	b) Analytical Procedures
	c) Validation of Analytical Procedures
	d) Batch Analysis
	e) Justification of Specifications
5.	Reference Standards or Materials
6.	Container Closure System
7.	Stability
PART III: NONCLINICAL DOCUMENT	
	Section A: Table of Contents
No.	Section B: Nonclinical Overview
1.	Overview of the Nonclinical Testing Strategy
2.	Pharmacology
3.	Pharmacokinetics
4.	Toxicology
5.	Integrated Overview & Conclusions
6.	List of Literature Citations
	Section C: Nonclinical Written and Tabulated Summaries
	Section D: Nonclinical Study Reports
	Section E: List of Key Literature References

PART IV: CLINICAL DOCUMENT	
	Section A: Table of Contents
No.	Section B: Clinical Overview
1.	Product Development Rationale
2.	Overview of Biopharmaceutics
3.	Overview of Clinical Pharmacology
4.	Overview of Efficacy
5.	Overview of Safety
6.	Benefits & Risks Conclusions
No.	Section C: Clinical Summary
1.	Summary of Biopharmaceutics Studies and Associated Analytical Methods
2.	Summary of Clinical Pharmacology Studies
3.	Summary of Clinical Efficacy
4.	Summary of Clinical Safety
5.	Synopses of Individual Studies
	Section D: Tabular Listing of all Clinical Studies
	Section E: Clinical Study Reports
	Section F: List of Key Literature References, Published Clinical Papers and Latest Periodic Safety Update Report (PSUR)

Notes:

- * Evaluated by Centre for Quality Control. For details, please refer to Section C: Quality Control in the main DRGD.

2.1.2 GENERAL REQUIREMENTS FOR ABRIDGED EVALUATION

No.	Step I: Product Validation
1.	Product Name
2.	Dosage Form
3.	Active Ingredient(s) a) Active Ingredient name b) Strength of Active Ingredient (Quantity unit per dose) c) Source of Active Ingredient (Animal – e.g. Bovine, Porcine, Ovine or Others/ Plant/ Others) d) Form of Active Ingredient e) Remarks (if any)
4.	Excipient(s) a) Excipient name b) Strength of Excipient (Quantity unit per dose) c) Function of excipient (e.g. absorbent, diluents, bulking agent, coating agent, anti-caking agent etc.) d) Source of excipient e) Remarks (if any)
5.	Is there any source of ingredients derived from animal origin, including active ingredient? (Yes/ No)
6.	Manufacturer (Name and Address)
7.	Is the selected manufacturer a contract manufacturer? (Yes/ No)
8.	Is the product from second source? (Yes/ No) If yes, please provide: a) Letter of declaration stating that this product is a second source product b) Registration number and product name of the first source
9.	Is this product containing any premix? (Yes/ No) a) State your premix form b) Manufacturer name c) Manufacturer address d) Certificate of Good Manufacturing Practice (GMP) e) Formulation f) Manufacturing Process g) Specification of Analysis h) Certificate of Analysis (CoA)

No.	Step I: Product Validation
10.	Is this a replacement product? (Yes/ No) If yes, please provide: a) Letter of Declaration stating that this product is a replacement product b) Registration number and product name of the replaced product
11.	Is there any other manufacturer (repacker)? (Yes/ No) a) Manufacturer (repacker) name b) Manufacturer (repacker) address c) Certificate of Good Manufacturing Practice (GMP) d) Packaging Process
12.	Is this an imported product? (Yes/ No)

Step II:	
No.	Section A: Product Particulars
1.	Product Name
2.	Product Description
3.	Dosage Form
	a) Source of Capsule Shell
	b) Certificate to verify the source of the capsule shell
	c) Coloring agent used in capsule shell (Please attach COA of the capsule shell)
4.	Product Indication/ Usage
5.	Dose/ Use Instruction
6.	Contraindication
7.	Warning and Precautions
8.	Drug Interaction
9.	Side Effects/ Adverse reaction
10.	Signs and Symptoms of Overdose and Treatment
11.	Storage Condition
12.	Shelf Life

Step II:	
13.	Therapeutic Code/ ATC Code
No.	Section B: Product Formula
1.	Batch Manufacturing Formula a) Batch Size b) Unit
2.	Active Ingredients a) Active Ingredients Name b) Quantity c) Source d) Form of Substance e) Overage (%) f) Remarks
3.	Excipients a) Active Ingredients Name b) Quantity c) Function d) Source e) Overage (%) f) Remarks
4.	Attachment of Batch Manufacturing Formula Documentation
5.	Manufacturing Process
6.	Attachment of Manufacturing Process Documentation
7.	In-Process Quality Control
8.	Attachment of Finished Product Specification Documentation
9.	Attachment of Stability Data Documentation (For two batches) - Compulsory for imported product
No.	Section C: Particulars of Packing - Please refer Appendix 10 : Guide for Implementation of Patient Dispensing Pack for Pharmaceutical Products in Malaysia
1.	Pack Size (Fill details by weight/ volume/ quantity) Measurement Type

Step II:	
2.	Immediate Container Type (Container Type and Description) e.g. Aluminium/ Glass/ Metal/ Paper/ Plastic/ Others
3.	Barcode/ Serial No. (Optional)
4.	Recommended Distributor's Price (RM) (Optional)
5.	Recommended Retail's Price (RM) (Optional)
6.	Other Related Attachment (if any)
No.	Section D: Label (Mock-up) For Immediate Container, Outer Carton, Proposed Package Insert - Please refer Appendix 9 : Labelling Requirements
1.	Proposed Label Mock-up for Immediate Container
2.	Proposed Label Mock-up for Outer Carton
3.	Proposed Package Insert
No.	Section E: Particulars of Product Owner, Manufacturer, Importer and Other Manufacturer(s) Involved and Store address
1.	Product Owner
2.	Manufacturer
3.	Other Manufacturer(s) involved (if any) a) Manufacturer Name and Address b) Processing Steps Involved c) Certificate of Good Manufacturing Practice (GMP)
4.	Store Name and Address
5.	Importer
No.	Section F: Supplementary Documentation
1.	Letter of Authorization from Product Owner
2.	Letter of Appointment of Contract Manufacturer from Product Owner (if applicable)
3.	Letter of Acceptance from Contract Manufacturer (if applicable)
4.	Is the active ingredient(s) patented in Malaysia? (If yes, please attach the related document)

Step II:	
5.	Certificate of Pharmaceutical Product (CPP)
6.	CPP Issuing Body
7.	Is this product licensed to be placed on the market for use in the exporting country? (If no, please state the reason)
8.	Is the product on the market in the exporting country? (If no, please state the reason)
9.	Date of Issue of CPP
10.	Date of Expiry of CPP
11.	Certificate of Free Sale (CFS) (if any)
12.	CFS Issuing Body
13.	Date of issue of CFS
14.	Date of expiry of CFS
15.	Certificate of Good Manufacturing Practice (GMP)
16.	Certificate of GMP Issuing Body
17.	Date of issue of Certificate of GMP
18.	Date of expiry of Certificate of GMP
19.	Summary of Product Characteristics (Product Data Sheet)
20.	Patient Information Leaflet (PIL)
21.	Attachment of Protocol Analysis
22.	Attachment of Certificate of Analysis (CoA) (For two batches) <i>* Compulsory for imported products</i>
23.	Attachment of Specifications and Certificate of Analysis of Active Ingredient
24.	Other Supporting Documents (if any)

2.1.3 ADDITIONAL INFORMATION ON:

A) BIOAVAILABILITY (BA) STUDY

For [modified-release products](#), dosage recommendations and regime must be supported by bioavailability studies.

Studies comparing availability or establishing equivalence of similar products would be useful.

B) BIOEQUIVALENCE (BE) STUDY

Note: *This requirement is applicable to generics (scheduled poison) only.*

With the increasing availability of generic products, a mechanism is required to ensure that such products are therapeutically equivalent to the innovators' products and are clinically interchangeable.

In practice, demonstration of bioequivalence (BE) is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products. A list of drug substances, which, when formulated in oral solid dosage forms, require BE data as a prerequisite for registration, has been established by the authority (please refer to BPFK website at <http://www.bpfk.gov.my>). This list is updated based on the requirements.

Bioequivalence (BE) Study Requirements for Generic Product in Immediate Release, Oral Solid Dosage Form Submitted as a Second Source Application

In general, for a second source application of a generic product (immediate release, oral solid dosage form), BE study report from the actual manufacturing site must be submitted during the submission of application for registration. The base of this requirement is due to the difference in manufacturing site from the first source that may change the characteristic and specifications of a second source product.

However, biowaiver can be considered, provided that Comparative Dissolution Profile (CPD) report against the registered first source product is submitted as a surrogate to bioequivalence study conducted for the second source product and all the following conditions shall be fulfilled:

- a) Bioequivalence study conducted using the registered first source product has been evaluated by the NPCB and found satisfactory.
- b) The second source product is the same as registered first source product used in the bioequivalence study in terms of:
 - i) Product formulation;
 - ii) Equipment used in the manufacturing process;
 - iii) Source and supplier of raw material;
 - iv) Quality control and specifications of raw material;
 - v) Manufacturing process of product and standard operating procedures;
 - vi) Environmental conditions during the manufacturing process of product;
 - vii) Quality control and specifications of finished product.
- c) Comparative Dissolution Profile must be conducted in accordance to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies including the calculation of similarity factor (f_2) to prove the similarity of these two products.
- d) Process validation has been conducted on 3 pilot or commercial batches of the second source product and found satisfactory by the NPCB.

This exemption is not applicable for any new submission of application for registration of a first source product. BE study must be conducted for this product which is manufactured at the actual manufacturing site submitted for registration.

(Reference: Circular [Bil.\(10\)d/m.BP/PPK/07/18Jld.1](#) , 2 Jun 2011)

Starting on 1st of January 2012, bioequivalence (BE) study is required for all application of registrations for generic products containing scheduled poison in the form of immediate release, oral, solid dosage form whereas renewal of registered products, the effective date is on 1st January 2013.

(Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Tahun 2011*, 2 March 2011 [Bil \(10\) d/m BP/PPK/01/03 Jld 1](#))

Sponsors or BE study centers are compulsory to notify the Authority pertaining to all BE studies which do not require Clinical Trial Import Licence (CTIL) or Clinical Trial Exemptions (CTX) and are going to be done at either local or overseas BE study centers for registered products or products to be registered in Malaysia (Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 13 Tahun 2011*, 14 October 2011, [Bil \(23\) d/m BP/PPK/01/03 Jld 1](#)).

Note: The two above directives shall be read in conjunction with the supplementary circular that further explains the procedure for evaluation of BE centre inspection reports in line with the requirement of accreditation of BE Centres. (Reference: Circular dated 12 September 2013; [Bil\(6\)dM.BPFIK/PPP/01/03 Jld 3.](#))

Effective 1st March 2013, biowaiver may be granted to generic immediate release oral solid dosage form products containing BCS Class I active ingredients listed in the Guidance On Biopharmaceuticals Classification System (BCS) – Based Biowaiver document. BCS Based biowaivers takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into accounts i.e. solubility and permeability of the drug substance/ API, and dissolution characteristics of the dosage form. This BCS approach provides an opportunity to waive *in vivo* pharmacokinetic bioequivalence testing for certain categories of immediate-release drug products.

(Directive *Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Tahun 2013*, 14 October 2011, 28 February 2013, Bil [\(101\)dM.BPFIK/PPP/01/03 Jld 2.](#))

For more information on BE, please refer [Bioequivalence \(BE\).](#)

2.2 SPECIFIC REQUIREMENTS

For biologics, health supplements and natural products, please refer guidelines for the respective product category at:

- a) [Appendix 3](#): Guidelines on Registration of Biologics
- b) [Appendix 4](#): Guideline on Registration of Health Supplements
- c) [Appendix 5](#): Guideline on Registration of Natural Products

Please refer as well on [Appendix 11](#): Guideline on Filling the Online Application Form for Product Registration via Quest System before submission of an application for product registration.

APPENDIX 3:

GUIDELINES ON REGISTRATION OF BIOLOGICS

IMPORTANT NOTES:

1. This document shall be read in conjunction with the relevant sections of the main guidance document: **Drug Registration Guidance Document (DRGD), which is in accordance to the legal requirements of the Sale of Drugs Act 1952 and the Control of Drugs and Cosmetics Regulations 1984.**
2. The National Pharmaceutical Control Bureau's (NPCB) requirements for registration of biologics/ biopharmaceuticals products are aligned with the scientific guidelines and recommendations for quality, clinical efficacy and safety and non-clinical of the World Health Organization (WHO), European Medicines Agency (EMA) and International Conference of Harmonization (ICH).
3. **Where appropriate, the relevant WHO, EMA and ICH guidelines on biologics/ biopharmaceuticals shall be consulted.**
 - WHO (<http://www.who.int/bloodproducts/en/index.html>)
 - EMA (<http://www.ema.europa.eu>)
 - ICH (<http://www.ich.org>)
4. **Every biologic is regulated as a new product and also considered 'high risk', it must** comply to Good Manufacturing Practice strictly. Adoption of GMP as an essential tool of Quality Assurance System.
5. The requirements for registration of biologics/ biopharmaceuticals shall be in accordance to the **ASEAN Common Technical Dossier (ACTD)** format and in adherence to the general regulatory requirement as described in sections of the main DRGD. It covers:
 - Administrative information
 - Product quality data
 - Product safety data
 - Clinical data, demonstrating clinical efficacy and capacity to meet therapeutic claims, through clinical studies.

6. Animal derived materials/ products are commonly used in the manufacture of biologics/ biopharmaceuticals. Please provide detail information regarding the rationale for use of such material, the source etc., as per **Checklist A** and **Checklist B**; and also provide a confirmation on the presence/ absence of the animal materials in the final product.
7. Since biosimilars are follow-on products of the original biopharmaceutical products (well-characterised recombinant proteins), this document also is applicable to biosimilars. Additionally, a separate [Guideline for Registration of Biosimilars](#) is available.
8. This document is intended to provide guidance for the registration of biologics. However, the document will serve as a living document that will be updated/ revised further in the line with the progress in scientific knowledge and experience.

Outline:

3.1 General Information

3.1.1 Definitions

3.1.2 Introduction

3.2 Specific Requirements for Registration of Biologics

3.2.1 Requirements for Registration of Biologics (Vaccines and Biotechnology Products)

a) Vaccines

i) Definition of Vaccine

ii) Requirements for Registration of Vaccines (Chemistry, Manufacturing And Controls, CMC)

b) Biotechnology Products

i) Definition of Biotechnology Product

ii) Additional Requirements for Registration of Biotechnology Products

c) References

3.2.2 Requirements for Registration of Blood Products

a) Definition of Blood Product

b) Requirements for Registration of Blood Products

c) Checklist of Plasma Master File for Blood Products

d) References

3.3 Checklists of Registration for Products Containing Materials of Animal Origin:

3.3.1 Checklist A: Products Containing Animal-Derived Materials **with**
a valid TSE risk evaluation Certificate of Suitability
(CEP)

3.3.2 Checklist B: Products Containing Animal-Derived Materials
without a valid TSE risk evaluation Certificate of
Suitability (CEP)

3.1 GENERAL INFORMATION

3.1.1 DEFINITIONS:

- i) **Biopharmaceutical/ Biotechnology Product**
- ii) **Biologic/ Biological Product**

- The term 'biopharmaceutical' was coined in the 80's to define proteins that were made by recombinant DNA technology [which includes hybridoma technology for monoclonal antibody (mAb) production].
- Biologic/ Biological product refers to a product whose active substance is made by or derived from a living organism (plant, human, animal or microorganism) and may be produced by biotechnology methods and other cutting-edge technologies. This product imitates natural biological substances in our bodies such as hormones, enzymes or antibodies.
- Biopharmaceuticals/ Biologics/ Biological products can also be defined as: "a protein (including antibodies) or nucleic acid-based pharmaceuticals used for therapeutic, which is produced by means other than direct extraction from a native (non- engineered) biological source". This corresponds to the new biotechnology view (that is, by elimination, it is largely restricted to recombinant/ genetically engineered and mAb-based products).
- The term 'Biotechnology product' and 'Biological product' are used to broadly refer to all biopharmaceuticals (by the broad biotechnology view).

Note: Today, biologics have become inextricably intertwined with biopharmaceuticals, to the point where they are synonymous. The general consensus is that a 'Biologic' and 'Biopharmaceutical' are interchangeable terminology, but a biologic might incorporate some other products (e.g. allergenics, somatic cells etc.).

Biologics include a wide range of products such as:

- Vaccines;
- Blood products;
- Monoclonal antibodies (therapeutics);
- Recombinant proteins:
 - Insulins
 - Hormones
 - Erythropoietins and other hematopoietic factors
 - Cytokines: interferons, interleukins, colony-stimulating factors, tumour necrosis factors.

But does not include:

- Metabolites from microorganisms; e.g antibiotics and some hormones.
- Macromolecules produced by chemical synthesis; e.g peptides/oligo-nucleotides produced by chemical synthesis.
- Whole blood or cellular blood components.

Note: *This document is not intended to apply to the control of genetically-modified live organisms designed to be used directly in humans, e.g. live vaccines.*

3.1.2 INTRODUCTION

It is acknowledged that biological substances used in the practice of medicines make a vital contribution to health care. Nevertheless, because of their nature, biologicals demand special attention with regard to their regulations to assure quality, efficacy and safety.

Biologicals are inherently variable due to their biological nature, produced from biological materials, and often tested in biological test systems, themselves variable, a feature that has important consequences for the safety and efficacy of the resulting product. Each product must be evaluated on its own merits. A prerequisite for the use of biological is therefore to assure the consistency of quality and safety from lot-to-lot.

Today, the biological field is one of enormous expansion and increasing diversity, most especially in the area of new biotechnologies. The revolution of DNA-based and other cell technologies has opened up a new and exciting vista, and in many instances, traditional products are being replaced by equivalents derived by recombinant DNA technologies or other cutting-edge technologies.

It is important to note that the demonstration that a product consistently possesses a desired characteristics of safety and efficacy will depend on a multifaceted approach on the part of manufacturer and the regulatory authority - drawing on thorough characterization of starting materials, demonstration of consistency of production, and appropriate selection of lot release tests - all under the stringent and documented controls imposed by good manufacturing practices - as well as rigorous post marketing surveillance activities.

3.2 SPECIFIC REQUIREMENTS FOR REGISTRATION OF BIOLOGICS

Specific requirements for registration of biologic/ biopharmaceutical are described as follows:

- Requirements for Registration of Biologics (Vaccines and Biotechnology products);
- Requirements for Registration of Blood Products.

3.2.1 REQUIREMENTS FOR REGISTRATION OF BIOLOGICS (VACCINES AND BIOTECHNOLOGY PRODUCTS)

a) VACCINES:

i) DEFINITION OF VACCINE

A vaccine contains an active component (the antigen). A vaccine is an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration or therapy of any disease or infection.

Vaccines for human use include one or more of the following:

- a) microorganisms inactivated by chemical/ physical means that retain appropriate immunogenic properties;
- b) living microorganisms that have been selected for their attenuation whilst retaining immunogenic properties;
- c) antigen extracted from microorganisms, secreted by them or produced by recombinant DNA technology; or
- d) antigen produced by chemical synthesis *in vitro*.

The antigens may be in their native state, truncated or modified following introduction of mutations, detoxified by chemical or physical means and/or aggregated, polymerized or conjugated to a carrier to increase immunogenicity. Antigens may be presented plain or in conjunction with an adjuvant, or in combination with other antigens, additives and other excipients.

**ii) REQUIREMENTS FOR REGISTRATION OF VACCINES
(CHEMISTRY, MANUFACTURING AND CONTROLS, CMC)**

A.	DESCRIPTION
	<ul style="list-style-type: none"> ▪ Description - Information on the source materials: source materials include any component/ unformulated active substance used in the manufacture of the product (e.g microorganisms, cells/ cell substrate, immunogen) including their specifications and the tests used to demonstrate compliance with the specifications. For combination vaccines, each active substance, which will be pooled, combined with other antigens and formulated, shall be described. ▪ Any chemical modification or conjugation of the drug substance shall be described in detail. ▪ List of inactive substances, which may be present in the drug substance.
B.	METHOD OF MANUFACTURE/ PRODUCTION
1.	<p>Manufacturing Formula:</p> <ul style="list-style-type: none"> ▪ List of all materials (culture media, buffers, resins for peptide synthesis, chemicals, columns etc.) and their tests and specifications, or reference to pharmacopoeia. ▪ Complete formula inclusive of any adjuvants, diluents, preservatives, additives, stabilisers etc. ▪ Production of each antigen in the vaccine (i.e. fermenter or culture volumes for each bulk batch size as applicable and typical bulk volumes per production run). ▪ Batch formula for each batch size and final formulated bulk product. ▪ Lot numbering system for intermediates and final product.
2.	<p>Manufacturing Process: Flow Charts/ Diagrams be Accompanied by a Descriptive Narrative:</p> <ul style="list-style-type: none"> ▪ Detailed description of manufacturing process and characterization of the product. Include complete history and characterization/ characteristics of each species, strain, cell banking systems - Master Cell bank (MCB) and Working Cell Bank (WCB), cell/ seed lot system, cell substrate system, animal sources (including fertilized avian eggs), virus source or cellular sources. <p>Ref: WHO TRS 878 (1998) <i>Annex 1: Requirements for the use of animal cells as in vitro substrates for the production of biologicals.</i></p> <ul style="list-style-type: none"> ▪ The flow chart should show the steps in production and a complete list of the in-

	<p>process controls and tests performed on the product at each step.</p> <ul style="list-style-type: none"> ▪ In-process holding steps, with time and temperature limits indicated. ▪ Description of the manufacturing processes (flow diagram) in detail to support the consistency of manufacture of drug substance - cell growth and harvesting. ▪ Identification of any processes or tests performed by contract manufacturers or testers. ▪ Animal cells: Cells of animal origin may harbour adventitious agents and consequently pose a potentially greater risk to humans. Description of measures taken to remove, inactivate, or prevent contamination of the product from any adventitious agent present. ▪ Information on measures to prevent any catastrophic events that could render the cell banks unusable and to ensure continuous production of vaccines is crucial. <p>For recombinant vaccines: description of the construction and characterization of the recombinant vector as well as source of master cell bank/ constructs.</p>
3.	<p>Process Validation Program:</p> <ul style="list-style-type: none"> ▪ Describe general policy for process validation and provide process validation activities performed.
4.	<p>Handling, Storage and Packaging:</p> <ul style="list-style-type: none"> ▪ All arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage.
C.	QUALITY CONTROL
1.	<p>Starting Materials:</p> <ul style="list-style-type: none"> ▪ List of all control tests performed on raw materials, with appropriate characterisation on starting materials. ▪ List of raw materials meeting compendia specifications. ▪ List of raw materials meeting in-house specifications including the tests performed and specifications ▪ Biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephalopathies (TSEs) and human diseases (HIV, hepatitis, etc) in the final product including Certificate of Suitability (CEP). <i>Please refer Checklist A & B</i> <p>Ref: WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical products (2010).</p>

2.	Intermediate Products (as appropriate): <ul style="list-style-type: none"> List the routine tests performed and specifications for intermediates.
3.	Finished Products (including diluents): <ul style="list-style-type: none"> List routine tests performed and specifications for final product. Description of the method and retest criteria.
4.	Analytical Validation Activities Performed: <ul style="list-style-type: none"> Include complete description of the protocol used for each bioassay, the control standards, the validation of inherent variability of test and the establishment of acceptance limits for each assay.
D.	STABILITY (http://www.who.int/biologicals/publications/trs/areas/vaccines/stability/en/)
	<ul style="list-style-type: none"> Information on stability of intermediates and final product, quality control methods and rationale for the choice of tests for determining stability. Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production. Describe the policy for assigning the date of manufacture of each component as well as the final product (e.g combination vaccine) and diluents, as appropriate. In addition to final product stability data at the recommended storage temperature, the accelerated stability data at elevated temperatures should be sufficient to justify the choice of Vaccine Vial Monitor (VVM) for use with the product [Vaccine Vial Monitor WHO/PQS/E06/IN05.1]
E.	LOT SUMMARY PROTOCOL AND LOT RELEASE FOR VACCINE
	<ul style="list-style-type: none"> Lot Summary Protocol - a document which describes the key steps and critical test results at each step of the production process must be submitted. Lot release is a basic principle in the control of vaccine. The aim of lot release is the confirmation of consistency of production as each lot of vaccine is unique. Submit Lot/ Batch Release Certificate issued by the competent authority. <p>Ref: <i>Guidelines for Independent Lot Release of Vaccines by Regulatory Authorities World Health Organization 2010</i></p>
F.	NONCLINICAL STUDIES FOR VACCINE
	<ul style="list-style-type: none"> Vaccines are a diverse class of biological products and their nonclinical testing programs will depend on product-specific features and clinical indications. Preclinical testing is a prerequisite to moving a candidate vaccine from the laboratory to the clinic and includes all aspects of testing, product characterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans.

	<ul style="list-style-type: none"> Some live attenuated vaccines must be tested for safety in animals before they are used in humans. <p>Ref: WHO TRS 927 (2005) <i>Annex 1: WHO guidelines on nonclinical evaluation of vaccines</i></p>
G.	CLINICAL STUDIES FOR VACCINE
	<ul style="list-style-type: none"> Clinical studies designed and conducted to meet WHO and international GCP principles. Tabulated summary of the clinical development program of the vaccine, in which critical parameters that may have changed during the clinical development. Copies of publications about these trials should accompany the submission. Clinical summary: Provide detailed summary and interpretation of the safety and efficacy data obtained from clinical studies that supports the current prescribing information. Clinical Expert Report: Provide an independent clinical expert report on the clinical studies (evidence of expertise and independence should be provided) <p>Ref:</p> <ul style="list-style-type: none"> WHO TRS 924 (2004) <i>Annex 1: WHO guidelines on clinical evaluation of vaccines:Regulatory expectations.</i> WHO TRS 850 (1995) <i>Annex 3: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products.</i>
H.	POST MARKETING SURVEILLANCE FOR VACCINES
	<ul style="list-style-type: none"> Provide an outline of the post marketing pharmacovigilance plan for the vaccine. Periodic safety update report (PSUR) in accordance to ICH Guideline E2C(R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. In the case of vaccines that have recently been registered/ licensed, provide information on any ongoing phase IV studies or on any active monitoring of the safety profile that is taking place including adverse events following immunization(AEFI). Risk management plan. <p>Please also refer to: NPCB's <i>Guidelines for Pharmacovigilance on Safety of Vaccines in Malaysia (January 2010)</i> ISBN 978-967-5570-05-6</p>

b) BIOTECHNOLOGY PRODUCTS**i) DEFINITION**

Biotechnological products includes the use of the new genetic tools of recombinant DNA to make new genetically modified organisms or genetic engineering products.

Products of recombinant technology are produced by genetic modification in which DNA coding for the required product is introduced, usually by means of a plasmid or viral vector into a suitable microorganism or cell line, in which DNA is expressed and translated into protein. The desired product is then recovered by extraction and purification.

ii) ADDITIONAL REQUIREMENTS FOR REGISTRATION OF BIOTECHNOLOGY PRODUCTS:

I.	PRODUCTION PROCESSES
	<ul style="list-style-type: none"> ▪ The production system shall be well defined and documented. ▪ The effectiveness of the overall purification process for active substance shall be demonstrated. ▪ Validation of procedures for removing contaminating cellular DNA, viruses and impurities.
J.	HOST CELL AND GENE CONSTRUCT
	<ul style="list-style-type: none"> ▪ Source of host cells, characterisation, stability, purity and selection. ▪ Information on gene construct, amino acid sequence, vector information and genetic markers for characterisation of production cells. ▪ Cloning process to form the final gene construct and mapping of sites used in constructions of final recombinant gene construct. ▪ Method of gene construct amplification and selection of recombinant cell.
K.	SPECIFICATIONS
	<ul style="list-style-type: none"> ▪ Drug substances should include assays for identity, purity, potency, physiochemical and stability. ▪ Identity and quantity of impurities along with analytical data which supports impurities profile ▪ Acceptable limits of impurities and should be included in the specifications if present in finished products.

L.	CHARACTERISATION
	<ul style="list-style-type: none"> Analytical testing performed to characterise the drug substance with respect to identity, purity, potency, and stability. Characterisation of drug substance include physiochemical characterisation, immunological properties and biological activity. Sufficient sequence information to characterise the product should be obtained. Post translational modifications should be identified and adequately characterised, especially when such modifications are likely to differ from those found in natural counterpart and may influence biological, pharmacological and immunological properties of the product.
M.	NONCLINICAL STUDIES
	<ul style="list-style-type: none"> Preclinical testing is a prerequisite to moving a candidate biotechnology products from the laboratory to the clinic and includes all aspects of testing, product characterization, proof of concept/ immunogenicity studies and safety testing in animals conducted prior to clinical testing in humans. The primary goals of nonclinical studies/preclinical safety evaluation are to identify an initial safe dose and subsequent dose escalation schemes in humans, potential target organs for toxicity (whether such toxicity is reversible) and safety parameters for clinical monitoring <p>Ref: ICH Topic S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.</p>
N.	CLINICAL STUDIES
	<ul style="list-style-type: none"> Clinical studies designed and conducted to meet WHO and international GCP principles. Overall approach to the clinical development of a medicinal product. Overview of the clinical findings and provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies. Interpretation of how the efficacy and safety findings support the proposed dose and target indication.

O.	POST MARKETING SURVEILLANCE FOR BIOTECHNOLOGY PRODUCT
	<ul style="list-style-type: none"> ▪ Provide an outline of the post marketing pharmacovigilance plan. ▪ Periodic safety update report (PSUR) in accordance to ICH Guideline E2C(R1) Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs. ▪ All relevant clinical and nonclinical safety data should cover the period of the report with exception of updates of regulatory authority or product registration holder (PRH) actions taken for safety reasons, as well as data on serious, unlisted adverse drug reactions (ADRs), which should be cumulative. ▪ Risk management plan

c) REFERENCES FOR VACCINES AND BIOTECHNOLOGY PRODUCTS:

i) Vaccines:

WHO (<http://www.who.int/biologicals/vaccines>)

i) WHO Technical Report Series: Vaccines

ii) Biotechnology Products:

WHO

- i) WHO Technical Report Series 1991 No. 814, Annex 3. Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. (*under revision*)
- ii) WHO Technical Report Series 1991 No 822, Annex 3. Guidelines for assuring the quality of monoclonal antibodies for use in humans.
- iii) WHO Technical Report Series No 878, Annex 1 and Addendum. Requirements for the use of animal cells as in vitro substrates for the production of biologicals.
- iv) WHO Technical Report Series No.786, Annex 3. Requirements for human interferons prepared from lymphoblastoid cells (Requirements for biological substances N0.42)
- v) WHO Technical Report Series No.771, Annex 7 Requirements for human interferons made by recombinant DNA techniques (Requirement for biological substance No. 41)

EMA

- i) CHMP/BWP/157653/07. Production and Quality Control of Monoclonal Antibodies and Related Substances.

- ii) CPMP/BWP/328/99. Development Pharmaceuticals for Biotechnological and Biological Products - Annex to Note for Guidance on Development Pharmaceuticals.
- iii) CHMP/BWP/157653/2007. Guideline on Development, Production, Characterisation and Specifications for Monoclonal Antibodies and Related Products.
- iv) EMEA/410/01 Rev. 3 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.

ICH

- i) ICH Topic Q5A Viral Safety Evaluation Of Biotechnology Products Derived From Cell Lines Of Human Or Animal Origin.
- ii) ICH Topic Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cell Lines used for Production of r-DNA derived Protein Products.
- iii) ICH Topic Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/ Biological Products.
- iv) ICH Topic Q5C Quality of Biotechnological products: Stability Testing of Biotechnological/ Biological Products.
- v) ICH Topic Q5D Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/ Biological Products.
- vi) ICH Topic Q5E Comparability of Biotechnological/ Biological Products Subject To Changes in Their Manufacturing Process.
- vii) ICH Topic Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products.
- viii) ICH Topic Q2 Validation of Analytical Procedures: Text and Methodology.
- ix) ICH Topic Q8 Pharmaceutical Development.
- x) ICH Topic Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/ Biological Entities).
- xi) ICH Topic S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.

3.2.2 REQUIREMENTS FOR REGISTRATION OF BLOOD PRODUCTS

Note: *This document is applicable to all plasma-derived products containing an active and inactive ingredient that is derived from human blood.*

a) DEFINITION OF BLOOD PRODUCT

Any therapeutic product derived from human blood or plasma and produced by a manufacturing process that pools multiple units.

Plasma-derived therapies and their recombinant analogs are unique among pharmaceuticals and biologics. Their production begins with a biological starting material, human plasma. Each therapy has a unique biochemical profile as a result of differences in production and processing methods that can lead to differing clinical responses and efficacy among patients.

Hence, from the starting material, through manufacturing and final distribution to patients, the complexities of producing blood products places it in a unique class of biologics.

Blood products are regulated as medicinal product. Blood products are inherently variable due to their biological nature, and the biological methods to test them. They are subjected to comprehensive assessment of the quality, efficacy and safety.

Four (4) principal complementary approaches are adopted:

- **Starting material:** Assurance of the quality and safety of the plasma for fractionation.
- **Manufacturing technique:** Control of the fractionation and subsequent manufacturing procedures for isolation, purification, viral inactivation and/or removal steps.
- **Good manufacturing practice (GMP):** Strict adherence to GMP. Adoption of GMP as an essential tool of Quality Assurance System.
- **Product Compliance:** Standardization of biological methods needed in characterisation of in-process and finished products.

Plasma for fractionation and blood products that are regulated by National Pharmaceutical Control Bureau (NPCB) includes:

- Plasma products derived from plasma collected and fractionated in Malaysia for use in Malaysia;
- Plasma products derived from plasma collected and fractionated overseas for use in Malaysia; and
- Plasma products derived from overseas-sourced plasma fractionated in Malaysia for use overseas.

b) REQUIREMENTS FOR REGISTRATION OF BLOOD PRODUCTS

1.	QUALITY OF PLASMA SOURCE MATERIAL
	<p>Plasma Master File (PMF). It can also be a stand-alone document. Document pertaining to the collection and controls of source materials. Key elements of PMF are:</p> <ul style="list-style-type: none"> ▪ Requirements for a formal contract governing purchase and supply of plasma. ▪ Source plasma. ▪ GMP status of the blood establishments/ collection centers. ▪ Description of the quality assurance system applying to plasma supply and use. ▪ Arrangements for donor selection, selection/exclusion criteria. ▪ Data on population epidemiology and blood-borne infections. ▪ Requirements for testing of samples of donations and pools. Mandatory serology on all plasma donations. Each unit of source material tested for HBsAg, anti-HIV and anti-HCV ▪ Plasma bags, plasma quality and plasma specifications. ▪ Arrangement for communication and review of post-donation information. ▪ Plasma inventory hold. ▪ Traceability from donor to end product and <i>vice versa</i>. <p>Ref: CHMP/BWP/3794/03 Rev. 1 Scientific data Requirements for Plasma Master File (PMF) and also the checklist.</p>

2.	MANUFACTURING PROCESS AND CONTROL
	<p>Documents that verify each batch of source material intended for manufacture has been serological tested for hepatitis B (HBV), hepatitis C (HCV) and HIV. Each batch of source material must also be tested for HCV RNA by Nucleic Acid Testing (NAT) and (increasingly for other viruses including HIV, HBV, B19, and HAV) and exclusion of reactive donations.</p> <p>Characterization: Physicochemical and biological characterization: Specific tests that will provide information regarding identity, purity, potency, stability and consistency of manufacture for the drug substance.</p> <p>Manufacture and Controls:</p> <p>i) Formula:</p> <ul style="list-style-type: none"> ▪ Include a list of all starting materials, reagents, monoclonal antibodies, intermediate products and auxiliary materials (buffers, sera, antibiotics etc.) with specifications or statement of quality for each. ▪ Excipients: List of excipients. ▪ For non-compendial excipients: Describe tests and specifications. ▪ For novel excipients: Include description for preparation, characterisation and controls. ▪ When used as excipient in the product, the expiry date of the plasma-derived product should not be earlier than that of the finished product. <p>ii) Manufacturing:</p> <ul style="list-style-type: none"> ▪ Detailed description of manufacturing process and controls to demonstrate proper quality control or prevention of possible contamination with adventitious agents. ▪ In-process and final controls. <ul style="list-style-type: none"> • Viral inactivation and/ or removal processes • Viral validation studies and report • Pathogen safety document inclusive of Transmissible Spongiform Encephalopathies (TSEs) risk assessment • Information or certification supporting the freedom of reagents, inactive ingredients of human or animal origin from adventitious agents. • Process consistency • Analytical validation studies • Process validation studies (purification, sterility etc.) • Batch record and batch release specifications

3.	THE FINAL PRODUCT
	<ul style="list-style-type: none"> ▪ Finished product testing and quality control ▪ Stability study program and expiration date ▪ Product history ▪ Container closure system, storage and handling ▪ Package insert and labels ▪ Lot/ batch release protocols ▪ Certificate of batch review and release from a competent authority
4.	CLINICAL STUDIES
	<ul style="list-style-type: none"> ▪ Demonstrating product's efficacy
5.	POST MARKETING SURVEILLANCE – mandatory follow-up
	<ul style="list-style-type: none"> ▪ Periodic Safety Update Report (PSUR) ▪ Risk Management Plans

c) Checklist of Plasma Master File for Blood Products

Section	Documents	Yes/No
1.	General Information	
1.1	Plasma Derived Products' List	
1.2	Overall Safety Strategy <ul style="list-style-type: none"> • Collection of plasma • Testing • Storage 	
1.3	General Logistics <ul style="list-style-type: none"> • Flowchart of supply chain of plasma 	
2.	Technical Information on Starting Materials/Plasma	
2.1	Plasma Origin <ul style="list-style-type: none"> • Information on Collection Centers • Information on Testing Centers • Selection/ Exclusion Criteria for Donors • Traceability 	
2.2	Plasma Quality and Safety <ul style="list-style-type: none"> • Compliance with Ph. Eur. Monographs or relevant monographs • Screening Tests for Markers of Infection • Technical Characteristics of Bags and Bottles for Blood and Plasma Collection, Including Information on Anticoagulant Solutions Used • Storage and Transport • Procedures for any Inventory Hold Period • Characterisation of the Fractionation Pool 	
2.3	Contract Between Manufacturer and Blood Collection Establishment(s) <ul style="list-style-type: none"> • System in place between the manufacturer and/or plasma fractionators/ processor on one hand, and blood collection establishments on the other hand which defines the conditions of their interaction and their agreed specifications 	

d) REFERENCES FOR BLOOD PRODUCTS:

The National Pharmaceutical Control Bureau's requirements for registration of blood products are aligned with the scientific guidelines and recommendations for quality, clinical efficacy and safety and non-clinical of the World Health Organization (WHO), European Medicines Agency and International Conference of Harmonization (ICH).

Where appropriate, the relevant WHO, EMA and ICH guidelines on blood products shall be consulted in particular the followings:

WHO (<http://www.who.int/bloodproducts/en/index.html>)

- i) WHO Technical report Series 941, Annex 4, Recommendations for production, control and regulation of human plasma for fractionation.
- ii) WHO Technical report Series 924, Annex 4, Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human plasma products.
- iii) WHO Guidelines on tissue infectivity distribution in Transmissible Spongiform Encephalopathies.

EMA (<http://www.ema.europa.eu>)

- i) EMA/CHMP/BWP/706271/2010 Committee for medicinal products for human use (CHMP) Guideline on plasma-derived medicinal products
- ii) CHMP/BWP/3794/03 Rev. 1 Scientific data Requirements for Plasma Master File (PMF)
- iii) CPMP/BWP/268/953AB8A Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses
- iv) EMEA/410/01 Rev. 3 Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products
- v) Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products, European Medicines Agency, EMA/CHMP/BPWP/144533/2009.
- vi) Note for Guidance on the Clinical Investigation of Human Plasma Derived Factor VIII and IX products, European Medicines Agency, CPMP/BPWG/198/95REV.1.
- vii) Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg), European Medicines Agency, EMA/VHMP/BPWP/94033/2007 REV.2.

ICH (<http://www.ich.org>)

- i) ICH Topic 5QC Quality of Biotechnological products: Stability Testing of Biotechnological/ Biological Products.

3.3 CHECKLISTS

3.3.1 Checklist A:

Products Containing Animal-Derived Materials **WITH** a valid TSE risk evaluation Certificate of Suitability (CEP)

No.	Documents	Yes/ No
1.	TSE Risk Evaluation Certificate of Suitability (CEP)	
2.	Basic information providing a brief description of the following:	
3.	Rationale for using animal-derived materials	
4.	Source of Animals <ul style="list-style-type: none"> • Declaration of materials of porcine origin • Declaration of materials of other animal origin 	
5.	Declaration of the nature of the animal tissue/ parts of animal used.	
6.	Description of the tissue/ organ-collection procedures and measures in place to avoid cross-contamination.	
7.	Nature and quantity of each animal-derived material used: <ul style="list-style-type: none"> • As a drug substance. • As an excipient or adjuvant. • As a starting material used in the manufacture of a drug substance. • As a starting material used in the manufacture of excipient. • As a reagent or culture media component used in manufacture. • As a reagent or culture media component used in establishing master cell banks. • As a reagent or culture media component used in establishing working cell banks. • Others, please provide details 	
8.	Declaration that the final product does not contain any animal-containing materials with the relevant evidence (if applicable)	
9.	Other supporting documents e.g. <i>Halal</i> Certification of the animal derived ingredient from a competent <i>Halal</i> Certification Authority.	
10.	Labelling of the animal derived materials.	

3.3.2 Checklist B:

Products Containing Animal-Derived Materials **WITHOUT** a valid TSE risk evaluation Certificate of Suitability (CEP)

Section	Documents	Yes/ No
1.	Detailed Assessment Report for the risk of TSE. The scope of this assessment report should include the following:	
2.	Rationale for using animal-derived materials	
3.	Source of Animals <ul style="list-style-type: none"> • Declaration of materials of porcine origin • Declaration of materials of other animal origin 	
4.	Declaration of the nature of the animal tissue/ parts used.	
5.	Description of the tissue/ organ-collection procedures and measure in place to avoid cross-contamination.	
6.	Detail of the risk factors associated with the route of administration and maximum therapeutic dosage of the product.	
7.	Nature and quantity of each animal-derived material used: <ul style="list-style-type: none"> • As a drug substance • As an excipient or adjuvant • As a starting material used in the manufacture of a drug substance. • As a starting material used in the manufacture of excipient. • As a reagent or culture media component used in manufacture. • As a reagent or culture media component used in establishing master cell banks. • As a reagent or culture media component used in establishing working cell banks. • Others, please provide details. 	
8.	Relevant information to support the claim that the manufacturing process is capable of inactivating TSE agents.	
9.	Certificates of analysis for each animal-derived materials used.	
10.	Declaration that the final product does not contain any animal-containing materials with the relevant evidence (if applicable)	

Section	Documents	Yes/ No
11.	Other supporting documents eg. Halal Certification of the animal derived ingredient from a competent Halal Certification Authority.	
12.	Labelling of the animal derived materials.	

APPENDIX 4:

GUIDELINE ON REGISTRATION OF HEALTH SUPPLEMENTS

IMPORTANT NOTES:

This guideline will serve as an additional reference guide for the registration of health supplement products which consist of pharmaceutical active ingredients for human use as well as ingredients derived from natural sources.

Applicants are advised to refer to Drug Registration Guidance Document for the common requirements for the preparation of a well-structured dossier application to be submitted for product registration.

Outline:

4.1 Definition

- 4.1.1 Health Supplement (HS)
- 4.1.2 Indication
- 4.1.3 Route of Administration
- 4.1.4 Exclusion as Health Supplement
- 4.1.5 Exemption

4.2 Active Ingredients

4.3 Maximum Daily Levels of Vitamins and Minerals for Adults Allowed in Health Supplements

4.4 Health Supplement Claim

- 4.4.1 Conditions
- 4.4.2 Types and Evidence of Claims
- 4.4.3 Claims Substantiation
- 4.4.4 Illustrative Substantiation Evidence

4.5 Specific Dossier Requirement for Registration of Health Supplements

Attachment 1: Checklist of Dossier Requirement for Health Supplements

Attachment 2: Table 20: Allowable Claims for Specific Active Ingredients in Health Supplements

Acknowledgements

4.1 DEFINITION

4.1.1 HEALTH SUPPLEMENT (HS)

A Health Supplement (HS) means any product that is used to supplement a diet and to maintain, enhance and improve the health function of human body. It is presented in small unit dosage forms (to be administered) such as capsules, tablets, powder, liquids and shall not include any sterile preparations (i.e. injectable, eyedrops). It may contain one or more, or the following combination:

- i) Vitamins, minerals, amino acids, fatty acids, enzymes, probiotics, and other bioactive substances;
- ii) Substances derived from *natural sources, including animal, mineral and botanical materials in the forms of extracts, isolates, concentrates, metabolite;
- iii) Synthetic sources of ingredients mentioned in (i) and (ii) may only be used where the safety of these has been proven.

4.1.2 INDICATION

- i) Used as a Health Supplement;
- ii) Vitamin and mineral supplements for pregnant and lactating women.

4.1.3 ROUTE OF ADMINISTRATION

Oral

4.1.4 EXCLUSION AS HEALTH SUPPLEMENTS:

Health Supplements shall NOT include:

- i) Any product as a sole item of a meal;
- ii) Any injectable and sterile preparation;
- iii) Any cells, tissues, organs or any substance derived from the human body;
- iv) Any substance listed in the Schedule of the Poison Act;
- v) Any other route of administration other than the oral route.

4.1.5 EXEMPTION

Extemporaneous preparations that have been prepared and given directly to the patient by a healthcare practitioner during the course of treatment.

4.2 ACTIVE INGREDIENTS

Listed active ingredients can be checked through <http://www.bpfk.gov.my> of product search.

4.3 MAXIMUM DAILY LEVELS OF VITAMINS AND MINERALS FOR ADULTS ALLOWED IN HEALTH SUPPLEMENTS

NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
1.	Vitamin A	5000 IU
2.	Vitamin D	1000 IU
3.	Vitamin E	800 IU
4.	Vitamin K (K1 and K2) ¹	0.12mg
5.	Vitamin B1 (Thiamine)	100 mg
6.	Vitamin B2 (Riboflavine)	40 mg
7.	Vitamin B5 (Panthothenic Acid)	200 mg
8.	Vitamin B6 (Pyridoxine)	100 mg
9.	Vitamin B12 (Cyanocobalamin)	0.6 mg
10.	Vitamin C (Ascorbic Acid)	1000 mg
11.	Folic Acid	0.9 mg
12.	Nicotinic Acid	15 mg
13.	Niacinamide (Nicotinamide)	450 mg
14.	Biotin	0.9 mg
15.	Boron	6.4 mg
16.	Calcium	1200 mg
17.	Chromium	0.5 mg
18.	Copper	2 mg
19.	Iodine	0.3 mg
20.	Iron ²	20 mg
21.	Magnesium	350 mg

NO.	VITAMINS & MINERALS	UPPER DAILY LIMIT
22.	Manganese	3.5 mg
23.	Molybdenum	0.36 mg
24.	Phosphorus	800 mg
25.	Selenium	0.2 mg
26.	Zinc	15 mg

Note:

1. *Vitamin K (K1 and K2) is restricted only for combination with other vitamins and minerals in oral preparations. Vitamin K (K1 and K2) as a single ingredient in an oral preparation is not allowed.*
2. *For pre and antenatal use, as part of a multivitamin and mineral preparation, levels higher than the 20mg limit established for adults may be permitted at the discretion of the Authority.*
3. *Any form of fluoride as an ingredient is not permitted in formulation of health supplement products.*

4.4 HEALTH SUPPLEMENT CLAIM

4.4.1 CONDITIONS

All claims made for HS shall:

- i) be consistent with the definition of HS;
- ii) enable consumers to make an informed choice regarding products;
- iii) not be misleading or false;
- iv) support the safe, beneficial and appropriate use of the product;
- v) maintain the level of scientific evidence which is proportional to the type of claims;
- vi) be for health maintenance and promotion purpose only;
- vii) not be medicinal or therapeutic in nature, such as implied for treatment, cure or prevention of disease.

4.4.2 TYPES AND EVIDENCE OF CLAIMS

- i) A health supplement claim refers to the beneficial effects of consuming HS to promote good health and well-being (physical and mental) by providing nutrition, enhancing body structure/ function, relieving physiological discomfort and/or reducing the risk of health related conditions or diseases.
- ii) Types of HS claims are:
 - General or Nutritional Claims;
 - Functional Claims (medium);
 - Disease Risk Reduction Claims (high).

- iii) For a HS product making a General or Functional Claim on vitamin(s) and/or mineral(s), it must contain minimum of 15% of the Codex Nutrient Reference Value (NRV) per daily dose of the vitamin(s) and/or mineral(s). Other ingredients must be substantiated by the evidences to which it has been supported.

For example, if vitamin is less than 15% NRV, then the specific claim for this vitamin is not allowed unless there is evidence to support effect below this value.

- iv) For a HS product making Disease Risk Reduction Claim, it must be substantiated by the evidences to which it has been supported.

(i) Table 1: General or Nutritional Claims

Level of claim	Definition	Examples/ Wording of claim	Criteria	Evidence to substantiate HS claims
General or Nutritional Claims	<ul style="list-style-type: none"> General Health Maintenance Benefits derived from supplementation beyond normal dietary intake 	<ul style="list-style-type: none"> Supports healthy growth and development Nourishes the body Relieves general tiredness, weakness Helps to maintain good health For energy and vitality For strengthening the body 	<ul style="list-style-type: none"> Is in line with established nutrition knowledge in reference texts Is related to general well-being in line with scientific knowledge Claim does not refer to the structure and/or function of the human body In accordance to HS principles and practice in Malaysia 	<p>1 or more of the following evidences:</p> <ul style="list-style-type: none"> i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs ii) Recommendations on usage from reference regulatory authorities or reference organisations

Please refer to Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

(ii) Table 2: Functional Claims (medium)

Claims must be adequately substantiated through ingredient-based evidence and when necessary through product-based evidence.

Types of HS claim	Definition	Examples/ Wording of claims	Criteria	Evidence to substantiate HS Claims
Functional Claims (medium)	<ul style="list-style-type: none"> ▪ Maintains or enhances the structure or function of the human body, excluding disease-related claims 	<p>Acceptable claims based on the single ingredient</p> <p>e.g.</p> <ul style="list-style-type: none"> ▪ Vitamin A helps to maintain growth, vision and tissue development ▪ Vitamin D helps in normal development and maintenance of bones and teeth. ▪ Chondroitin helps to promote healthy joints 	<p>For claims on established nutrients and ingredients such as vitamins & minerals with daily recommended values</p> <ul style="list-style-type: none"> ▪ Meet the conditions for nutrient function claims as set by the Authority ▪ Claims have consistent scientific support according to scientific review and evaluation ▪ In accordance to HS principles and practice in Malaysia 	<p>1 or more of the following evidence:</p> <ul style="list-style-type: none"> i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs ii) Recommendations on usage from reference regulatory authorities or reference organisations iii) Good quality scientific evidence from human observational studies (refer to ASEAN Guidelines on efficacy data requirement) (only in the event that human experimental study is not ethical, animal studies will be accepted together with epidemiological studies or other scientific literature and documented traditional use) iv) Peer-reviewed scientific data or meta-analysis

Please refer to Illustrative Substantiation Evidence List for the list of acceptable references, organisations and authorities.

(iii) Table 3: Disease risk reduction (high)

Types of HS claim	Definition	Examples/ Wording of claims	Criteria	Evidence to substantiate HS Claims
Disease risk reduction	<ul style="list-style-type: none"> Significantly altering or reducing a risk factor of a disease or health related condition. 	<ul style="list-style-type: none"> Helps to reduce risk of osteoporosis by strengthening bone Helps to reduce the risk of dyslipidaemia 	<ul style="list-style-type: none"> The relationship between the HS ingredient or product and disease risk reduction is supported by consistent scientific evidence Documented in authoritative reference texts Recognised by the Authority reference or international organisations or regulatory authorities Adheres to the key principles of HS claims 	<p>Compulsory evidence:</p> <ul style="list-style-type: none"> i) Scientific evidence from human intervention study on ingredient and/or product ii) Toxicological study (chronic) iii) Pharmacological study <p>At least 1 additional evidence:</p> <ul style="list-style-type: none"> i) Standard reference e.g. reference textbooks, pharmacopoeia, monographs etc. ii) Recommendations on usage from reference regulatory authorities or reference organisations iii) Evidence from published scientific reviews or meta-analysis iv) Report prepared by expert committees/ expert opinion (subject to the Authority approval)

Please refer to *Illustrative Substantiation Evidence List* for the list of acceptable references, organisations and authorities.

4.4.3 CLAIMS SUBSTANTIATION

Claims must be in line with the respective HS principles and supported by adequate evidence. To reflect the total available usage evidence (including relevant scientific evidence), the evidence shall be summarized as part of the substantiation document for the claim as in the **Table 4** below.

Indication/ claim	Product/ Ingredient studied	Dosage and administration route	Duration of treatment	Type of evidence (scientific evidence)	Study design	Study population	Summary of findings	Limitations of the study	Source of evidence i) Author ii) Title iii) Publication details iv) Year v) Type (text,...)

Note: Evidence not summarised as in the above format will not be further evaluated.

4.4.4 ILLUSTRATIVE SUBSTANTIATION EVIDENCE

i) Reference texts

- a. Martindale, latest edition. The Complete Drug. Pharmaceutical Press, 2009.
- b. The ABC Clinical Guide to Herbs. American Botanical Council
- c. WHO Monographs on Selected Medicinal Plants
- d. British Pharmacopoeia
- e. United States Pharmacopoeia
- f. Indian Pharmacopoeia
- g. Chinese Pharmacopoeia
- h. Natural Standards (www.naturalstandard.com)
- i. Office of Dietary Supplements, National Institutes of Health - Dietary Supplement Fact Sheets
([http://ods.od.nih.gov/Health Information/Information About Individual Dietary Supplements.aspx](http://ods.od.nih.gov/Health%20Information/Information%20About%20Individual%20Dietary%20Supplements.aspx))

ii) Organisations

- a. American Botanical Council (www.herbalgram.org).
- b. American Nutraceutical Association (www.ana-jana.org)
- c. CODEX Alimentarius
- d. Global Information Hub for Integrated Medicine (<http://www.globinmed.com>)
- e. National Centre for Complementary and Alternative Medicine (<http://nccam.nih.gov/>)
- f. Office of Dietary Supplements, National Institutes of Health (USA)
(<http://ods.od.nih.gov>)

iii) Reference regulatory authorities

- a. Australia TGA
- b. Chinese Health Authority on Chinese medicinal herbs
- c. European Commission
- d. Health Canada
- e. United States FDA

Notes:

1. *This list is not meant to be exhaustive and will be reviewed from time to time.*
2. *The Authority will nonetheless conduct a detailed evaluation of the evidence included in the report to ensure that the health claim is substantiated.*
3. *The Authority will be willing to consider review other than the listed above, if the standards of evidence are consistent with those of the Authority.*
4. *All references must be current.*

4.5 SPECIFIC DOSSIER REQUIREMENT FOR REGISTRATION OF HEALTH SUPPLEMENTS

PRODUCT VALIDATION

1. PRODUCT NAME

- May include product name, dosage form and strength (e.g. XYZ Capsule 500mg)
- Dosage form and strength of product would need to be entered as part of product name to allow for multiple dosage forms (e.g. tablet, capsule) and strengths (e.g. 200mg and 400mg) for any particular named (proprietary or generic) product.
- In any event if found that registered product name is similar to another registered product, NPCB reserve the rights to request for the change in the product name.
- Product with more than 1 active ingredient could not include strength of active ingredients in the product name.
- Product name may be included together with the brand name or trademark name, if applicable.
- Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product is prohibited.

Table 5: List of Non-Permissible Product Name for Health Supplement Products

No.	Issue	Example
1.	Prohibited use of disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (revised 1983)	Diabetes, Asthma, Cancer
2.	Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika	If the product contain Vitamin C, Vitamin E and Fish Oil Product name: "Vitamin C" is not allowed but product name: "Vitamin C Plus" is allowed.

No.	Issue	Example
3.	Prohibited use of superlative Names which indicates superiority inefficacy	Power, Superior, Pure, Mustajab, Safe, Healthy, Penawar, VIP, Good, World Number 1
4.	Prohibited use of spelling of words which may cause confusion i) Words which involve names of/part thereof: 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) ii) Other diseases without scientific proof iii) Prohibited indication	Go Out = GOUT (label) Utix
5.	Prohibited use of names which may cause ambiguity Ambiguous product name	B For Energy?
6.	Prohibited use of names which may be offensive or indecent	SENXBIG=SEnXBIG(label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire
7.	Product name which is not congruent with the active ingredient.	The active ingredient is Evening Primrose oil (EPO) and the product name: "Marine tablet" is not allowed.
8.	Prohibited use of product names which has elements of ludicrous belief Statements referring to ancient believe/negative spirits/supernatural power	Words such as miracle, magic, magical, miraculous, saintly, heavenly

No.	Issue	Example
9.	Prohibited use of product names similar to the existing approved product names Product name similar to the spelling and pronunciation of words of an existing product names	Elegen vs L-gen vs L-jen Forte vs Fort
10.	Prohibited use of product names which may cause ambiguity in the nature of product (drug/ food/ beverage) Product name similar to a food/ beverage name	Juice, Health drink, Beverage, Kooky
11.	Prohibited use of product names which represents professional advice or opinion	Dr Sunny, Professor
12.	Product name that symbolize a claim	Vigour, Youthful, High, Hi
13.	Product name that uses strength but formulation contains more than one active ingredient.	If the product contains multivitamins and minerals. Product name: “XXX multivitamins and minerals 500mg” is not allowed.
14.	Other prohibited product names	Minda, IQ, Smart, Unique, Ultra Mega, Detox
15.	Names of organs and brain	Heart, kidney, skin, liver

Note:

1. This list is not meant to be exhaustive and will be reviewed from time to time.
2. The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual.

2. DOSAGE FORM

- Dosage forms allowed:
 - a) Tablets
 - Caplet, Lozenge, Chewable tablet, Dispersible tablet, Effervescence tablet, uncoated tablet, enteric coated tablet, Sugar coated tablet, Film coated tablet, extended release tablet;
 - b) Capsules
 - Soft capsule, Hard capsule, Enteric coated capsule, Chewable soft capsule, Extended released capsule;
 - c) Powder/ Granules;
 - d) Liquid
 - Emulsion, syrup, spray, suspension.
- Products in the shape of animal dosage forms are not allowed.
- Supporting data from established reference (e.g. Standard Pharmacopeia) shall be required for new dosage form.
- The form that correctly describes it in terms of its product quality control specifications and performance shall be selected.
- A separate application for registration is required for each dosage form.
- The following documents will have to be provided during submission of product dossier for **Sustained-release/ Extended-release/ Timed-release dosage form**
 - i) Protocol of analysis;
 - ii) In-Process Quality Control (IPQC);
 - iii) Finished Product Specification (FPQC);
 - iv) Certificate of Analysis (COA).

3. ACTIVE INGREDIENT

Name of Active Ingredient:

- Please select active ingredient from the search database. If substance is not listed, please select the 'Not Listed Ingredient' button. Automatic e-mail will be send to NPCB for notification.
- Approved names, pharmacopoeia names of ingredients shall be used whenever possible.

Strength of active ingredient :

- To enter the content of active ingredients (numerical) and then select the weights and measures from the given list.
- Content of ingredients shall be expressed as appropriate in the following manner:
 - a. quantity per dose unit (e.g. for unit dose formulations - tablet, capsule, lozenge, etc.)
 - b. percentage composition - %w/w, %w/v, %v/v, etc.
 - c. weight per ml. (e.g. for solutions, suspension etc.)
 - d. quantity (percentage or amount) per measured dose (e.g. oral liquids, drops, etc.)
- Metric weights and measures shall be used.

Source of Active ingredient:

- To specify the source such as animal, plant, synthetic or others (to specify)

Remarks on active ingredient (if any):

- To specify the equivalent/providing amount of active component from the raw material (e.g: Sodium ascorbate 520 mg providing.... Vitamin C)
- Declaration of species name from natural source (plant, animal or others)

Table 6: Additional data to support a new health supplement active ingredients:

No.	Types of documents	Checklist
1.	Standard/ established references	<ul style="list-style-type: none"> • Martindale, Pharmacopeias, Monograph etc.
2.	Information from the competent authorities of reference countries	<ul style="list-style-type: none"> • Information shall be provided from the competent authorities of reference countries (Refer to 9.6.5) • Example of supporting documents: <ul style="list-style-type: none"> ➤ Registration status and maximum registered dosage as health supplement ➤ established monograph ➤ GRAS status

No.	Types of documents	Checklist
3.	Clinical studies or scientific evidences	<ul style="list-style-type: none"> • Full published articles • Unpublished data may be considered • Mandatory for high claim
4.	Non-clinical studies to support long term-use	
5.	Toxicology studies with the determination of NOAEL (No observed adverse effect level)	
6.	Pharmacological study	
7.	Justification for the use of new active ingredient as health supplement	
8.	Registration status worldwide	<ul style="list-style-type: none"> • Registered and Marketed Date

Note: The documentation must support the safety use and dose of new active ingredients as a health supplement.

4. ANY ANIMAL ORIGIN

Any source from animal origin must be declared and to specify the type of animal.

5. MANUFACTURER

Manufacturer is defined as “A company that carries out at least one step of production as well as the final release of the finished product”.

The requirements for Good Manufacturing Practice (GMP) of the premises are in **Table 7** as followed:

Level of claims	Requirements for GMP
General/ Functional	<p>a) <i>Malaysia Guidelines on Good Manufacturing Practice for Traditional Medicine and Health Supplement latest edition.</i></p> <p style="text-align: center;">Or</p> <p>b) The accepted standards for GMP will be determined by the category the product is classified in the country of origin. For example, if the product is classified as food in the country of origin, GMP certificate of food standard issued by relevant country authority will be accepted on condition that the standards are similar to those practices in Malaysia.</p> <p style="text-align: center;">Or</p> <p>c) If the product is not regulated in the country of origin and does not require GMP certification, the manufacturer will have to produce a GMP certificate issued by an independent body recognised by the Authority. Information including the standard/ regulations/ legislation to which the inspection was based upon must be mentioned.</p>
Disease Risk Reduction	<p>a) <i>Malaysia Guidelines on Good Manufacturing Practice for Traditional Medicine and Health Supplement latest edition</i></p> <p style="text-align: center;">Or</p> <p>b) The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) Standards.</p> <p style="text-align: center;">Or</p> <p>c) GMP certificates issued by relevant country authority will be accepted on condition that the standards are similar to PIC/S Standards</p>

6. CONTRACT MANUFACTURER

Contract manufacturer is applicable when product owner is not the product manufacturer

7. SECOND SOURCE INFORMATION

An application for a second source may be considered where deemed necessary. This second source product shall be the same as the first product in all respects except for the site of manufacture.

8. PRODUCT CONTAINING PREMIX

Premixed active ingredient(s) is a combination of two or more active ingredients that are previously manufactured by a different manufacturer.

Certificate of GMP for manufacturer/ supplier is required for the premixed ingredient(s) in formulation. The requirements for GMP are same as in Field 5 as above.

9. REPLACEMENT PRODUCT

A product registration holder is not allowed to register/ hold two or more products with similar formulation (same active ingredient of raw material, strength and dosage form) at any one time unless product variant.

Letter of justification for replacement by product holder is required.

10. OTHER MANUFACTURER

Any manufacturer involved in Assembly, Fill & Finish, Active Ingredients, Packing, Labeling etc.

11. IMPORTED PRODUCTS

Imported product needs to be declared.

SECTION A: PRODUCT PARTICULARS

- **Product Description:**

State, briefly, **visual and physical characteristics** of the product, including as in the following **Table 8** (where applicable):

No.	Dosage Form	Description
1.	Tablet	Shape, size, colour, odour, taste, marking, emboss, type of tablet (e.g. coated, uncoated, film, sugar etc.)
2.	Capsule	Shape, size, colour, odour, taste, marking, emboss, coating, content of capsule, type of capsule (e.g.: soft, hard, chewable etc.)
3.	Liquid	Clarity, type (e.g. solution/ suspension/ emulsion etc.), taste, odour, colour.
4.	Powder	Colour, odour, taste etc.
5.	Pill	Colour, odour, taste, size etc.
6.	Granules	Colour, odour, taste, size etc.

- **Indication/ Usage**

State briefly recommended use(s) of product. The following indications are allowed:

- Used as a Health Supplement; or
- Vitamins and mineral supplements for pregnant and lactating women.

- **Recommended Dose (Dose/ Use Instruction) & Route of administration**

State the dose (normal dose, dose range) and dosage schedule (frequency, duration if applicable). Dosage for adults and children (where appropriate) shall be stated.

- **Contraindication**

State conditions for which or under which the product shall not be used.

Note 1: Indicate clearly which conditions are:

- absolutely contraindicated,
- contraindicated but may be used under special circumstances and what precautions to be taken in such cases.

- **Warnings and Precautions**

State briefly precautions and warnings necessary to ensure safe use of the product e.g. caution against giving to children and elderly; use in pregnancy and lactation; in infants; etc.

- **Drug Interactions**

State only interactions which are observed and/or for which there is potential clinical significance. Interactions may occur with

- other medicinal products used;
- other herbs/ substance;
- meals, or specific types of food.

- **Side Effects/ Adverse Reactions**

State in order of severity and frequency, the side effects, adverse reactions, toxic effects, etc. (i.e. reactions, toxic effects, other than those desired therapeutically) including reactions such as allergy, hypersensitivity, dependence, addiction, carcinogenicity, tolerance, liver/ kidney toxicity etc.

Indicate also symptoms and sites of effects/reactions.

Note 1 : Reactions, whether minor or serious, shall be stated.

Note 2 : Severity, reversible, frequency of occurrence shall be indicated wherever possible.

Note 3 : Clinical tests for detection of 'sensitive' patients, measure for management of adverse reactions developed shall be described wherever possible.

- **Pregnancy and Lactation**

Please state any effect on pregnancy and lactation if applicable.

- **Signs and Symptoms of Overdose and Treatment**

State briefly symptoms of overdose/ poisoning, and where possible, recommended treatment and antidotes for overdose/ poisoning.

- **Storage Conditions**

State the recommended storage conditions (specific temperature eg: 30°C, humidity, light etc.).

Information shall also include storage condition before first opening, after reconstitution and/or after opening and for all the listed pack types where applicable. Stability data to support such storage condition shall be available.

- **Shelf Life**

The shelf life for all the listed pack types shall be supported by stability data.

Information shall also include shelf life before first opening, after reconstitution and/or after opening where applicable. Stability data to support such shelf life shall be available.

Evidence is required to demonstrate that the product is stable (meets the finished product shelf life specifications throughout its proposed shelf-life).

- **Therapeutic Code (If any)**

Please select “Health Supplement”

SECTION B: PRODUCT FORMULA

- Change of formulation whether for active ingredient or excipient is not allowed during product evaluation.

- **Batch Manufacturing Formula**

State the batch size and actual batch manufacturing master formula. Data from validation step will be captured in terms of substance name, type (active ingredient or excipient), function and quantity per unit dose. Other information will need to be entered.

An **attachment** of the Batch Manufacturing Formula documentation must be provided. The documents must be verified by authorized personnel.

Example of BMF documentation:

ABC Sdn. BHD. Batch Manufacturing Formula				
Product Name: Batch Quantity: 1,000,000 capsules				
Name	Function	Quantity per capsule	Batch quantity	Overage
Pyridoxine HCl	Active	_ mg	_ kg	_ %
Cholecalciferol	Active	_ mg	_ kg	_ %
Glycerin	Excipient	_ mg	_ kg	None
Gelatin	Excipient	_ mg	_ kg	None
Purified water	Excipient	0 mg *	_ kg	None
		Total: _ mg	Total: _ kg	
* evaporated, does not exist in final formulation (Signature) Post of authorized person Name of authorized person Date:				

- **Manufacturing process**

State a brief description of the manufacturing process. Essential points of each stage of manufacturing process and a description of the assembling of the product into final containers shall be covered. If the product is repacked/assembled by another manufacturer, details of repacking/assembly and quality control must be supplied.

An **attachment** of the manufacturing process, in the form of a flow chart can be made.

- **In Process Quality Control (IPQC)**

To provide a summary of the tests performed, stages at which they are done, and the frequency of sampling and number of samples taken each time. Specifications for quality assurance of the product shall be supplied.

Example of In Process Quality Control:

Company Name/ Address:

Applicant/ Client Name/ Address:

Date:

In-Process Quality Control: Test performed during manufacturing process

No.	Test Done (example)	Stage Done (example)	Frequency of testing (example)	Quantity sample taken (example)	Specifications (example)	Method (example)
1.	Appearance	Before weight, after encapsulation	2	10 gram	Blue like orange	Organoleptic test
2.	Disintegration	After compression	2	10 tablet	NMT 30 minutes	Equipment etc
3.	Uniformity of weight	After tableting, Packaging	4	20 Tablets	1 gram/tab	
4.	Microbiology	Final Stage	1			
5.	Heavy metal	Final stage	1			

* Declaration (if any)

Signature (authorized personnel)

Name:

Designation:

*** The above parameters are only as an example; other test may be required for specific product.**

- **Finished Product Quality Specification**

Provide details of quality control specifications including a list of tests for both release and shelf life specifications (if they are different) and state the limits of acceptance.

Example of Finished Product Quality Specification

Finished Product Quality Control (FPQC) - Finished product Specification/ Specification Sheet				
Company name/Address:				
Product Name:				
Batch no.				
Dosage form:				
Packaging:				
Date of manufacture:				
Date of expiry:				
No.	Test	Method	Specification	Reference
1.	Appearance/ Organoleptic: Odour Colour	Ex: Macroscopic/ Microscopic	To describe the characteristic	In-house/ pharmacopoeia (e.g. BP/USP etc)
2.	Assay: List the active ingredients	HPLC/ GC/ MS/ UV	To specify	To specify
3.	Disintegration/Dissolution	To specify	DRGD	DRGD
4.	Uniformity of weight	To specify		
5.	Water content	To specify		
6.	Microbial contamination TAMC, TYMC, specified microorganism	To specify	DRGD	DRGD
7.	Heavy Metal Contamination: Lead, Arsenic, Cadmium, Mercury	To specify	DRGD	DRGD
8.	Etc:			
Signature:				
Name:				
Designation: (At least by Quality Assurance Manager or equivalent)				
Date of signature:				
* The above parameters are only as an example; other test may be required for specific product.				

• **Stability Data**

Table 9:

No.	Stability Study	Shelf Life
1.	<p>i) 2 batches of complete real-time stability study at 30 ± 2 °C / RH $75 \pm 5\%$ for the claimed shelf-life.</p> <p style="text-align: center;">OR</p> <p>ii) 2 batches of on-going real time stability study (at least 6 months) at 30 ± 2 °C / RH $75 \pm 5\%$ + Letter of commitment (LOC) to submit complete real time stability data when study is complete/ when requested.</p> <p style="text-align: center;">AND</p> <p>2 batches of 6 months accelerated stability study at 40°C.</p>	<p>- Shelf life will be based on data stability at 30°C of not more than 5 years.</p> <p>- 3 years</p>
2.	<p>i) 2 batches of complete real time stability study at a temperature and relative humidity (RH) different from the Zone IVB for at least 2 years + LOC to conduct real time stability study at Zone IVB and submit when the study is complete/ when requested</p> <p style="text-align: center;">OR</p> <p>ii) 2 batches of on-going real time and accelerated stability study (at least 6 months) at a temperature/ relative humidity (RH) different from Zone IVB + LOC to conduct real time stability study at Zone IVB and submit when the study is complete/ when requested.</p>	<p>- Shelf life will be based on data stability at specified temperature.</p> <p>- 2 years at specified temperature in the stability study.</p>
3.	<p>2 batches of complete real-time stability study at temperature and RH other than zone IVB for very unstable active ingredient(s)/ product (must be substantiated).</p>	<p>- Shelf life will be based on data stability at specified temperature.</p>

Storage Conditions with Type of Container Closure System/ Stability Study**Table 10:**

No.	Type of Container Closure System/ Study	Storage Condition
1.	Products in primary containers permeable to water vapour	$30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{RH}$
2.	Products in primary containers impermeable to water vapour	$30^{\circ}\text{C} \pm 2^{\circ}\text{C}$
3.	Accelerated studies	$40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{RH}$

Reports of stability studies shall provide details of:

- the batches placed under study (a minimum of 2 batches are required).
- containers/ packaging type.
- conditions of storage during study (temperature, humidity, etc).
- duration of study and frequency (interval) of the tests/ observations.
- the tests performed and acceptance limits.

Example of Stability Data**STABILITY DATA****PRODUCT NAME:** TABLET ABC 500MG**BATCH NO.:****MANUFACTURING DATE:** dd/mm/yy**TEMPERATURE:** 30 °C ± 2 °C**EXPIRY DATE:** dd/mm/yy**RELATIVE HUMIDITY:** 75 % ± 5%

Tests	Specification	Frequency of Testing								
		0	3	6	9	12	15	18	21	24
Product description	Film-coated tablet, brownish in colour									
Disintegration test	NMT 30 minutes									
Assays	eg: 90% -120% (ref....)									
Microbial Contamination test:										
Total Aerobic Microbial Count	NMT 2 x 10 ⁴									
Total Yeasts & Moulds Count	NMT 2 x 10 ²									
Test for Specified Microorganisms	<ul style="list-style-type: none"> ➤ NMT 2 x 10² CFU of bile-tolerant gram-negative bacteria in 1g or 1ml ➤ Absence of Salmonella in 10g or 10ml ➤ Absence of Escherichia coli in 1g or 1ml ➤ Absence of Staphylococcus 									
Heavy metal test:										
Lead	≤10.0 mg/kg (≤ 10ppm)									
Arsenic	≤5.0 mg/kg (≤ 5ppm)									
Mercury	≤0.5 mg/kg (≤ 0.5ppm)									
Cadmium	≤0.3 mg/kg (≤ 0.3ppm)									

Conclusion -----

Analyst name: (signature)

Verified by: (signature)

Name:

Name:

Designation

Designation

Date:

Date:

Stability study data checklists are as in **Table 11** below:

Data Required	Remarks
Company name	- From product holder/ manufacturer/ third party lab
Product name	- To be same with other documentation
Dosage form	- To be same with A3
Packaging particulars	- Material and pack size must be stated - To be same with C1
Storage condition	- Temperature and humidity must be stated - Shall comply with ASEAN Zone IV requirement (30±2°C/75±5%RH) - If different storage condition (e.g. 25°C, 2-8°C), must provide justification/ supporting data.
Frequency of testing	For example: - 0, 3, 6, 9, 12, 18, 24 months and annually for the proposed shelf life
List of relevant tests	- All tests required for each dosage form shall be conducted, for example: <ul style="list-style-type: none"> ○ Physical appearance changes ○ Disintegration test (if applicable) ○ Chemical Assays for active ingredients (if applicable) ○ Microbial tests
Specifications	- Acceptance limit for each test must be stated - To be supported by established references (e.g. USP, BP) if available
Results for each test	- Must meet the specifications
Approval by authorized person	- Must have the name, post and signature of authorized person

Testing Parameters of Stability Study for each type of dosage forms are shown in **Table 12** below:

Testing Parameters Dosage Form	Appearance/ organoleptic (odor, color, taste)	Assay	Hardness/ friability	Disintegration or dissolution rate	Moisture content	Viscosity	pH	Microbial content	Granules/ Particle Size variation	Re-suspendability
Oral powder	√	√			√			√		
Hard capsule	√	√		√	√			√		
Soft capsule	√	√		√				√		
Coated and Uncoated Tablet	√	√	√ (uncoated)	√	√			√		
Coated and Uncoated Pill/ Pellet	√	√		√	√			√		
Suspension	√	√				√	√	√	√	√
Solution	√	√				√	√	√		
Emulsion	√	√				√	√	√		
Granules	√	√			√			√	√	

***Notes:**

1. The list of tests for each product is not intended to be exhaustive, nor is it expected that every listed test to be included in the design of the stability study protocol for a particular finished product.

* Assay to determine the stability of a single active ingredient or a single marker/surrogate indicator that is susceptible to change during storage and is likely to influence quality shall be sufficient to infer the overall stability of the TM/HS product irrespective of whether the finished product contains single or multiple active ingredients.

2. Justification must be given if one of the tests is not conducted for relevant dosage form.

SECTION C: PARTICULARS OF PACKING

- **Packaging**
 - Maximum pack size allowed for tablets, pills, capsules is based on daily dosing for a quantity not exceeding six (6) months usage.
 - Maximum pack size allowed with disease risk reduction claim for 1 month supply of products unless justified.
 - Product with dosage form of softgel with tail (twist and squeeze) shall come with children proof cap.
- Packing particulars to the listing of packing as follows ;
 - C1: pack size and fill details by weight, or volume or quantity;
 - C2 : container type
 - C3 : Barcode/ serial No (optional);
 - C4 : recommended distributor's price (optional);
 - C5 : recommended retail price (optional);

SECTION D: LABELLING REQUIREMENTS

- **Label (mock-up) for immediate container, outer carton**

Outer Unit Carton, Immediate & Blister/ Strips Labels

*The following information in **Table 13** shall be present on the label of the product:*

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
1.	Product Name	✓	✓	✓
2.	Dosage Form	✓	✓*	NA
3.	Name of Active Substance(s)	✓	✓	✓**
4.	Strength of Active Substance(s)	✓	✓	✓**
5.	Batch Number	✓	✓	✓
6.	Manufacturing Date	✓	✓*	NA
7.	Expiry Date	✓	✓	✓
8.	Route of Administration	✓	✓	NA
9.	Storage Condition	✓	✓*	NA
10.	Country's Registration Number	✓	✓*	NA
11.	Name & Address of Product Registration Holder (PRH)	✓	✓*	Name/ Logo of Manufacturer/ Product Owner
12.	Name & Address of Manufacturer	✓ At least name of town/ city and country of manufacturer	✓* At least name of town/ city and country of manufacturer	NA
13.	Warnings and/or Specific Labelling (if applicable)	✓	✓*	NA

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
14.	Pack Sizes (unit/ volume)	✓	✓	NA
15.	Name & content of preservative(s) where present	✓	✓	NA
16.	Name & content of alcohol, where present	✓	✓	NA
17.	To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine (capsule shell).	✓	✓	NA
18.	Recommended daily allowance (RDA) for vitamins/ multivitamins/ mineral preparations used as dietary supplements	✓	✓	NA
19.	The words “Keep medicine out of reach of children” or words bearing similar meaning in both <i>Bahasa Malaysia</i> & English	✓	✓*	NA
20.	Other country specific labelling requirements (if applicable)	✓	✓*	NA
21.	Security Label (Hologram)	✓#	✓*	NA

Notes:

- NA - Not applicable
- ** For multi-vitamins and minerals preparations it is suggested to label as multi-vitamins and minerals
- If the product is without an outer carton, the inner label shall bear all the information that is required
- Information on the Product Name and Name and Strength of active ingredient(s) must be printed repeatedly.
- # In case of no outer carton, the security label shall be applied to the immediate labels. The security label shall not be applied onto outer shrink wrap of a product.

- **Package inserts (Optional)**

The following information is required to be included in a package insert:

- (i) Brand or Product Name
- (ii) Name and Strength of Active Substance(s)
- (iii) Product Description
- (iv) Indication
- (v) Dose/ Use Instruction
- (vi) Contraindications
- (vii) Warnings and Precautions
- (viii) Interactions with Other Medications
- (ix) Statement on usage during pregnancy and lactation
- (x) Adverse Effects/ Undesirable Effects
- (xi) Overdose and Treatment
- (xii) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
- (xiii) Dosage Forms and packaging available
- (xiv) Name and Address of manufacturer/ product registration holder
- (xv) Date of Revision of Package Insert

- **Standard Labelling for Health Supplements**

<ul style="list-style-type: none"> • Name and Strength of active substances, RDA • Preservative(s) (where present) • Alcohol (where present) • Indication • Dose / Use Instruction • Functional Claim • Warnings (If applicable) • Storage Condition • Keep out of reach of children / Jauhi dari kanak-kanak 	<div style="border: 1px solid black; border-radius: 15px; padding: 10px; text-align: center; margin: 10px;"> <p>PRODUCT NAME</p> </div> <div style="border: 1px solid black; border-radius: 50%; padding: 10px; text-align: center; margin: 10px;"> <p>GRAPHIC</p> </div> <div style="display: flex; justify-content: space-around; margin-top: 10px;"> <ul style="list-style-type: none"> • Pack Size • Dosage Form </div>	<ul style="list-style-type: none"> • Name & address of Marketing Authorization Holder • Name & address of Manufacturer • Name & address of Repacker (if applicable) • Sources (animal origin) • Batch Number • Manufacturing Date • Expiry Date
MAL		

Note:

- *Product label shall follow the standard labelling for Health Supplement*
- *Information stated in the left and right panel is interchangeable.*
- *All information on the label must be truthful and not misleading to the consumers.*
- *Batch number, manufacturing date, expiration date: can be stated on label, on top of cap or bottom of bottle*

- **Additional Requirements for Labelling**

- Product with dosage form of soft gel with tail (twist and squeeze) shall include the statement 'Under parent supervision' in the label.
- For products containing animal origin(s), please add this statement: *This product contains substance(s) from animal origin.*
- For products containing porcine, please add this statement: *This product contains animal part(s) (porcine/pig).*

- Health supplement products with disease risk reduction claims (high) are encouraged to be dispensed under the supervision of pharmacists or medical practitioners. At such, the label and package insert of health supplement products with disease risk reduction claims (high) shall have the following statement:

“Please consult a healthcare professional before taking this product”.

- The front panel must contain the information as specified in DRGD. However, the information on the side panels is interchangeable. Additional cautionary labelling relating to the safety of the product may be imposed.

- **Specific Labelling Requirement (Label & Package Insert)**

1. ALFALFA

The following boxed warning shall be included on the labels of products containing **Alfalfa** (*Medico sativa*):

This product contains **Alfalfa** (*Medico sativa*).
Individual with a predisposition to **systemic lupus erythematosus** shall consult their physician before consuming this product.

2. ARGININE

The following statement shall be included on the labels and in the package insert of oral preparations containing Arginine for **health supplements**:

WARNING:

Arginine is not recommended for patients following a heart attack.

3. ASPARTAME

The following statement shall be included on the labels and in the package insert of products containing Aspartame:

WARNING:

Unsuitable for phenylketonurics

4. BEE POLLEN

The following statement shall be included on the labels and in the package insert of product containing bee pollen:

- This product contains Bee Pollen and may cause severe allergic reactions, including fatal anaphylactic reactions in susceptible individuals.
- Asthma and allergy sufferers may be at greater risks.

5. CHITOSAN

The following statement shall be included on the labels and in the package insert of products containing chitosan.

“DERIVED FROM SEAFOOD”

6. GINKGO BILOBA/ GINKGO EXTRACT

The following statements shall be included on the labels and in the package insert of products containing **Ginkgo Biloba/ Ginkgo Extract**:

As the use of Ginkgo may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/ dental procedure.

(Memandangkan Ginkgo boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau/ akan menggunakan ubat lain dan sebelum prosedur pembedahan/ dental dijalankan).

7. GINSENG

The following statements shall be included on the labels and in the package insert of products containing Ginseng (including all Panax genus):

- Contraindicated in pregnant women.
- Safe use in lactating women and children has not been established.
- Do not exceed the stated dose.
- Safety on long term use has not been established.

8. INGREDIENTS DERIVED FROM SEAFOOD

The following statement shall be included on the labels and in the package insert of products.

“DERIVED FROM SEAFOOD”

9. ROYAL JELLY

This product contains royal jelly and may cause severe allergic reactions including fatal anaphylactic reactions in susceptible individuals.

Asthma and allergy sufferers may be at the greater risk.

10. SODIUM METABISULPHITE (Excipient)

The following statement shall be included in the package insert of products containing Sodium metabisulphite:

WARNING:

This preparation contains Sodium metabisulphite that may cause serious allergic type reactions in certain susceptible patients. Do not use if known to be hypersensitive to bisulphites.

- **Prohibited Visual/ Graphics on Label**, as shown in **Table 14** below:

No.	Issue	Example	Note
1.	Marketing strategy	Example: “Money back guarantee” “Buy 1 free 1” “Backed by RM5 million product Liability Insurance”	Such statements are prohibited on labels, as per Medicines (Advertisement and Sale) Act 1956 requirements
2.	Usage guide which promotes use of other product(s)	Example: “After consumption of this product (Product A), for better results, it is recommended to take Product B”	Prohibited on product label
3.	Consumer testimonial		Prohibited on product label

No.	Issue	Example	Note
4.	Clinical Trial results or any information on clinical trial done on product	Example : “Clinically Tested” “Randomized Double Blind Placebo Control Clinical Study”	Such statements are prohibited on labels (as per Medicines (Advertisement and Sale) Act 1956 Requirement
5.	Reference to Hadith/ Al-Quran/ Bible/ Religious books		Prohibited on product label
6.	Opinion of prominent figure(s) on product or its active ingredient/ content	Example: Opinion of product/formulation inventor	Prohibited on product label
7.	Label design (graphic and color) similar to labels from another company		Prohibited on product label
8.	Statement on active ingredient origin	Example: Source from the Mountains of Alps	Allowed if proven true
9.	Introduction of founder/ Manufacturer		Prohibited on product label
10.	Logo with certification	Example: SIRIM/ ISO / GMP/ HACCP	Prohibited on product label because certification renewal is on a yearly basis

No.	Issue	Example	Note
11.	Name/ Statement/ Logo/ registered trademark which does not satisfy the specifications	Example: “Dr.ABC’s Formula” “Nothing like it”	Prohibited on product label
12.	Patency claim/ Patency number/ Special technique used/ superiority in ingredients (Example: capsule coat)	Example: Patented technique	Allowed if proven true
13.	Nutritional claims with analysis certificate attached	Example: Calorie, Fat, Protein and others	Prohibited on product label
14.	Graphics or picture of internal organs	Example: Kidney, Heart, Nerves.	Prohibited on product label
15.	Sex symbol (male or female)	(♀ and/or ♂)	Prohibited on product label
16.	Indecent photographs/ pornography		Prohibited on product label
17.	Graphics which are incoherent with the indication	Example: - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose.	Prohibited on product label

No.	Issue	Example	Note
18.	Highlighting unnecessary body parts	Example: Indication is for general health but graphics on label highlights male and female sexual organ parts	Prohibited on product label
19.	Graphics of plants or animal which may cause confusion	Example: Radix Ginseng which is improvised as a male sexual part	Prohibited on product label
20.	Other statements	Example: - This product is blended with premium quality - Certified chemical residue free	Prohibited on product label

Notes:

1. This list is not meant to be exhaustive and will be reviewed from time to time
2. The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual

SECTION E: PARTICULAR OF PRODUCT OWNER, MANUFACTURER, IMPORTER AND OTHER MANUFACTURER

- Please select whether the product owner is the product holder, manufacturer or both product holder and the manufacturer.
- If the product owner is neither product holder nor the manufacturer, please select name and address of the product owner (applicable for imported product only).
- Other details such as Section E1: Product Owner, Section E2: Manufacturer, Section E3: Repacker, Section E4: Other manufacturer involved in the manufacturing process, Section E5: Store address and Section E6 Importer (If any) have to filled. It is mandatory for the Repacker to acquire GMP certificate.

SECTION F: SUPPLEMENTARY DOCUMENTS

- **Letter of authorization of product owner**

This is applicable for imported product in which the product owner appoints the product holder (in Malaysia) as their product holder in Malaysia

- **Letter of appointment of contract manufacturer and/ or repacker**

Applicable if the product is contract manufactured by a manufacturer who is not the product holder.

- **Letter of acceptance as contract manufacturer and/ or repacker**

Applicable if the product is contract manufactured by a manufacturer who is not the product holder.

- **Certificate Of Pharmaceutical Product (CPP), Free Sale Certificate (CFS) and Good Manufacturing Practice (GMP)**

CPP can be attached as a replacement of CFS and GMP certificate if the product is classified as pharmaceutical product in the country of origin:

GMP/ CFS Template

Authority name, address, country

Type of certificate

Company name (product owner/ manufacturer)

Product name

Product formulation if available

Dosage form

Statement of freely sold (similar meaning) if for CFS certificate

Standard of GMP and compliance status if for GMP certificate

Duration of certification

Name, signature and designation of authorized personnel

Date of signature

Note: The certificate must be in English or translated into English
(certified true by issuance or embassy or notary public)

• **Attachment of Protocol Analysis**

Protocol analysis is attached here.

• **Finished Product Quality Control (FPQC)**

- The certificate must be complete with the product specification and result. The list of tests and specifications must be same with finished product specification document.
- Quality Control Test For Health Supplement Product are as follows:

1. Limit Test for Heavy Metals

- a) Lead : NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm)
- b) Arsenic : NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm)
- c) Mercury : NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm)
- d) Cadmium : NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm)

** Required for products with ingredients from natural sources.*

The test shall be conducted either on the raw material or finished product.

2. Disintegration Test (for tablets, capsules and pills)

Disintegration time:

- a) Uncoated tablets : NMT 30 minutes
- b) Film-coated tablets : NMT 30 minutes
- c) Sugar-coated tablets : NMT 60 minutes
- d) Enteric-coated tablets : Does not disintegrate for 120 minutes in acid solution but to disintegrate within 60 minutes in buffer solution
- e) Capsules : NMT 30 minutes
- f) Pills : NMT 120 minutes

3. Test for Uniformity of Weight (tablets and capsules only)

i) Tablet

- For tablet with average weight of 130mg or less: Not more than 2 tablets differ from the average weight by more than 10% AND no tablets differ from the average weight by more than 20%
- For tablet with average weight between 130-324mg: Not more than 2 tablets differ from the average weight by more than 7.5% AND no tablet differs from the average weights by more than 15%
- For tablets with average weight more than 324mg: Not more than 2 tablets differ from the average weight by more than 5% AND no tablet differs from the average weight by more than 10%

ii) Capsule

Individual weight of the capsule to be within the limit of 90-110% of the average weight.

4. Tests for Microbial Contamination, as shown in Table 15 below:

Route of Administration	TAMC (CFU/g or CFU/ml)	TYMC (CFU/g or CFU/ml)	Specified micro-organisms
Non-aqueous preparations for oral use	10^3	10^2	Absence of <i>Escherichia coli</i> (1 g or 1 ml)
Aqueous preparations for oral use	10^2	10^1	Absence of <i>Escherichia coli</i> (1 g or 1 ml) Absence of <i>Burkholderia cepacia</i> (1 g or 1 ml)
Oromucosal use	10^2	10^1	Absence of <i>Staphylococcus aureus</i> (1 g or 1 ml) Absence of <i>Pseudomonas aeruginosa</i> (1 g or 1 ml) Absence of <i>Burkholderia cepacia</i> (1 g or 1 ml)
Special Ph. Eur. provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU per gram or per millilitre	10^4	10^2	Not more than 10^2 CFU of bile-tolerant gram-negative bacteria (1 g or 1 ml) Absence of <i>Salmonella</i> (10 g or 10 ml) Absence of <i>Escherichia coli</i> (1 g or 1 ml) Absence of <i>Staphylococcus aureus</i> (1 g or 1 ml) Absence of <i>Burkholderia cepacia</i> (1 g or 1 ml) – for aqueous preparation only
Special Ph. Eur provision for herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced and powdered): - herbal medicinal products to which boiling water is added before use - herbal medicinal products to which boiling water is not added before use	10^7 10^5	10^5 10^4	Not more than 10^2 CFU of <i>Escherichia coli</i> (1 g or 1 ml) Not more than 10^3 CFU of bile-tolerant gram-negative bacteria (1 g or 1 ml) Absence of <i>Escherichia coli</i> (1 g or 1 ml) Absence of <i>Salmonella</i> (10 g or 10 ml)

Notes:- **Abbreviation:**

TAMC : Total Aerobic Microbial Count

TYMC : Total Yeasts & Moulds Count

NMT : Not more than

- **Interpretation of the results as follows:** 10^1 CFU : maximum acceptable count = 20; 10^2 CFU : maximum acceptable count = 200; 10^3 CFU : maximum acceptable count = 2000, and so forth.

- **Specifications and Certificate of Analysis of Active Ingredient**

Certificate of analysis for each active ingredient (raw material) is required pre-registration. The certificate must consist of specifications and results of analyses.

- **Other Supporting documents**

- For the submission of other supporting documents.
- Additional requirement for safety and quality of active ingredient/ product (e.g.; dose for children, pregnant etc.)
- Quality testing for specific ingredient:
 - For product containing *Aphanizomenon flos-aquae*, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method
- Quality testing for specific product:
 - Certificate of Analysis for Dioxin level is required for product containing ingredient(s) derived from seafood
 - Certificate of Analysis for proof of hormone-free is required for product containing placenta

ATTACHMENT 1

CHECKLIST OF DOSSIER REQUIREMENT FOR HEALTH SUPPLEMENTS

- Depending on the level of claims, submission may follow the route as outlined:
 - General/ Nutritional and Medium Claims - Abridge evaluation
 - Disease Risk Reduction Claims - Full evaluation

Table 16: Checklist for General/ Nutritional and Medium Claim

No.	Field	General or Nutritional Claims	Functional Claims
A1	Product Name	√	√
	Brand name and product name		
A2	Product Description	√	√
	- Describe visual and physical characteristics of the product including shape, size, superficial markings, colour, odour, taste, type of coating, type of capsule etc where applicable		
	- Animal shape is only allowed for 'For Export Only' (FEO) Products		
A3	Dosage Form	√	√
	- COA capsule shell is required		
	- Source of capsule shell		
	- BSE/ TSE free certificate if capsule from animal source from competent authority		
	- Letter to rectify the source of gelatine from the product manufacturer		
	- Colouring agent used in capsule		
A4	Product indication/ Usage	√	√
A5	Dose/ Use Instruction	√	√
	- Quantity and frequency		
	- Dosing schedule must be stated (e.g. take before/ after/ with meal)		
A6	Contraindication, if applicable	√	√
A7	Warning/ Precautions, if applicable	√	√

No.	Field	General or Nutritional Claims	Functional Claims
A8	Drug Interaction, if applicable	√	√
A9	Side Effects/ Adverse Reactions, if applicable	√	√
A10	Signs and Symptoms of overdose and treatment, if applicable	√	√
A11	Storage Condition	√	√
	- According to stability data		
A12	Shelf life	√	√
	- Must be supported by stability study - Please refer to B5		
A13	Therapeutic Code	√	√
	- As a health supplement		
B1.1	Batch Manufacturing Formula	√	√
B1.2	List of Active ingredient(s)	√	√
	- BSE/ TSE free certificate if active ingredient from animal source		
B1.3	List of excipient(s)	√	√
B1.4	Attachment of Batch Manufacturing Formula	√	√
	- Shall be on the product owner's/ manufacturer's original letterhead, product details, date and signature & designation of authorized personnel		
B2.1	Manufacturing Process	√	√
B2.2	Attachment of Manufacturing Process Document or Manufacturing Flow Diagram	√	√
B3	In-Process Quality Control (IPQC)	√ *LOC to submit data during post registration	√

No.	Field	General or Nutritional Claims	Functional Claims
B4	Finished Product Specification (FPQC)	√ * LOC to submit data during post registration	√
B5	Stability Data (Please refer page 24)	√	√
D1	Label for immediate container	√	√
D2	Label for outer carton (if applicable)	√	√
D3	Proposed package insert / Product information leaflet (if applicable)	√	√
E1	Company name and address of product owner	√	√
E2	Company name and address of manufacturer(s)	√	√
E3	Company name and address of repacker (if applicable)	√	√
E4	Company name and address of other manufacturer (if applicable)	√	√
E5	Store address(s)	√	√
E6	Importer(s)	√	√
F1	Letter of authorization from product owner to product registration holder (if applicable)	√	√
F2	Letter of Appointment of Contract Manufacturer/ Repacker from Product Owner (if applicable)	√	√
F3	Letter of Acceptance from Contract Manufacturer/ Repacker (if applicable)	√	√
F4	Certificate of Pharmaceutical Product (CPP) - Applicable to imported products, must be issued by the competent authority in the country of origin. CPP issued by reference country may be considered.	√	√

No.	Field	General or Nutritional Claims	Functional Claims
F5	Certificate of Free Sale (CFS) - Applicable if CPP is not available, must be issued by the competent authority in the country of origin/ products owner country.	√	√
F6	Certificate of Good Manufacturing Practice (GMP) - Applicable if CPP is not available, must be issued by the competent authority in the manufacturing country.	√	√
F9	Attachment of protocol analysis	√ - dosage form extended release * LOC to submit during post for other types of dosage form	√ - dosage form extended release - validation of analytical method for new actives or new combination dosage
F10	Attachment of Certificate of finished product (COA of finished product)	√ * LOC to submit during post registration	√
F11	Attachment of Specifications and Certificate of Analysis (COA) of Active Ingredient	√	√
F12	Examples of supporting documents		
	Dioxin level test results (for product containing ingredients derived from seafood)	√	√
	Certificate of Good Manufacturing Practice (GMP) for premixed active ingredients		
	Hormone free test results (for placenta products)		
	Declaration letter from product manufacturer on the hormone - free status for product containing placenta		

No.	Field	General or Nutritional Claims	Functional Claims
	Manufacturing process validation report if applicable		
	Letter of commitment if applicable		
	Etc.		
<p>* Complete stability study conducted at 30 ± 2 °C / RH 75 ± 5%, IPQC, FPQC, protocol analysis and COA of finished product are required to be submitted 2 years after product registration with SAMPLE of the products. Failure on submission will cause the product be suspended until the complete documents are submitted, the registration of the product will be terminated if the complete documents still cannot be produced upon renewal of product registration.</p>			

- Dossier Requirement for Disease risk reduction as in **Table 16 above** and **Table 17** below:

Table 17: Additional Quality Data Checklist for Disease Risk Reduction Claim

No.	Field	Disease Risk Reduction Claim
PART P	P. HEALTH SUPPLEMENT PRODUCT P1. <u>Description and Composition</u> P2. <u>Pharmaceutical Development</u> P2.1 Information on Development Studies P2.2 Components of the Health Supplement Product P2.3 Finished Product P2.4 Manufacturing Process Development P2.5 Container Closure System P2.6 Microbiological Attributes P2.7 Compatibility P3. <u>Manufacturer</u> P3.1 Batch Manufacturing Formula P3.2 Manufacturing Process & Process Control P3.2.1 Manufacturing Process Flowchart P3.3 Control of Critical Steps & Intermediates P3.4 Process Validation and Evaluation P4. <u>Control of Excipients</u> P4.1 Specifications P4.2 Analytical Procedure P4.3 Validation of Analytical Procedures P4.4 Justification of Specification P4.5 Excipient of Human or Animal Origin P4.6 Novel Excipients P5. <u>Control of Finished Product</u> P5.1 Specification P5.2 Analytical Procedures P5.3 Validation of Analytical	√

No.	Field	Disease Risk Reduction Claim
	Procedures P5.4 Batch Analyses P5.5 Characterization of impurities P5.6 Justification of Specification P6. <u>Reference Standards or Materials</u> P7. <u>Container Closure System</u> P8. <u>Stability</u> P9. <u>Product Interchangeability/Equivalent evidence</u>	
PART S	S. HEALTH SUPPLEMENT SUBSTANCE S1. <u>General Information</u> S1.1 Nomenclature S1.2 Structure S1.3 General Properties S2. <u>Manufacture</u> S3. <u>Characterisation</u> S4. <u>Control of Health Supplement Substance</u> S4.1 Specification S4.2 Analytical Procedures S4.3 Validation of Analytical Procedure S4.4 Batch Analysis S4.5 Justification of Specification S5. <u>Reference Standards or Materials</u> S6. <u>Container Closure System</u> S7. <u>Stability</u>	√

PART III: NON-CLINICAL DATA

- Applicable to disease risk reduction claims
(For new active ingredient, new combination of active ingredients and new dose)

Table 18:

No.	Field	Disease Risk Reduction Claims
1.	Overview of non-clinical testing strategy	√
	- nomenclature	
	- structure	
	- general properties	
2.	Pharmacology	√
	- related information (including academic literature) of pharmacology studies on the declared efficacy	
3.	Pharmacokinetics	√
	- related information (including academic literature) of pharmacokinetics studies on the declared efficacy	
4.	Toxicology	√
	- related information (including academic literature) of toxicology studies	
5.	Integrated overview and conclusions	√
6.	Other toxicity studies if available	√
7.	References	√
	- List of references used	

- All information must be provided in the following format/ table:

Study Title	Type of Study	Product (formulation)	Study Summary <ul style="list-style-type: none"> - Study Design (e.g. case control, randomised placebo controlled, in vitro data, cohort study) - Dosage - Subject - Study Duration - Outcome parameters 	Summary findings (Includes scientific details such as strength of evidence [e.g. p-values], conclusions, any shortcomings, etc. For traditional evidence include enough information to demonstrate relevance)

PART IV: CLINICAL DOCUMENTS

- Applicable to disease risk reduction claims (for new active ingredient, new combination of active ingredients and new dose).

Table 19:

No.	Field	Disease Risk Reduction Claims
1.	Clinical overview	√
2.	Production Development Rational	√
3.	Overview of Bio-pharmaceutics	√
	- To include associated analytical methods	
4.	Overview of Clinical Pharmacology	√
	- Summary of clinical pharmacology studies	
5.	Overview of Efficiency	√
	- Summary of clinical efficacy	
6.	Overview of Safety	√
	- Summary of clinical safety	
7.	References	√
	- List of all clinical studies	
	- List of key literature references	
	- Published clinical papers	

- All information must be provided in the following format/table:

Forms of study	Sample size	Duration	Randomisation of groups	Endpoint	Statistical analysis of data
Randomised, controlled, and preferably blinded intervention studies	Must be justified and must involve sufficiently large number of subjects to estimate incidence and nature of potential adverse reactions	Must be justified and must be of sufficient duration to ensure no safety concerns with respect to long term use	All groups shall have comparable baseline values, particularly for those factors that are known to be, or may be, confounders or risk factors	As a decrease incidence of the disease or a reduction of a factor, or a surrogate thereof, of the many that contribute to the development of a disease	Methods to calculate the sample size, setting the power and the significance level at conventional 80% and $p < 0.05$ respectively shall be utilised Meta-analysis shall combine only studies with similar design, populations, interventions and outcome measure

ATTACHMENT 2

Table 20: Allowable claims for specific active ingredients in HS products

Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Vitamin A	<ul style="list-style-type: none"> Maintenance of good health 	<ul style="list-style-type: none"> Helps to maintain growth, vision and tissue development Aids in maintaining the health of the skin and mucous membrane 	
Vitamin C		<ul style="list-style-type: none"> For healthy bones, (cartilage), teeth, gums as well as general make-up of the body 	
Vitamin D	<ul style="list-style-type: none"> Maintenance of good health 	<ul style="list-style-type: none"> Helps in normal development and maintenance of bones and teeth Helps the body utilize calcium and phosphorus Claim for specific population subgroups: Elderly people who are confined indoors 	
Vitamin E	<ul style="list-style-type: none"> Maintenance of good health 		

Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Beta Carotene	<ul style="list-style-type: none"> Maintenance of good health 	<ul style="list-style-type: none"> Helps in maintenance of growth, vision and tissue differentiation 	
Vitamin B1 (Thiamine)	<ul style="list-style-type: none"> Helps to maintain good health 	<ul style="list-style-type: none"> Helps in maintenance of growth, vision and tissue differentiation 	
Riboflavin (Vitamin B2)	<ul style="list-style-type: none"> A factor in maintenance of good health 	<ul style="list-style-type: none"> Helps the body to utilize energy from food/ metabolize protein, fats and carbohydrates Claim for specific population subgroups: <ul style="list-style-type: none"> -Additional amounts of Riboflavin are required during pregnancy and breast feeding when diet does not provide a sufficient daily intake 	
Niacin (Vitamin B3)	<ul style="list-style-type: none"> A factor in maintenance of good health 	<ul style="list-style-type: none"> Helps normal growth and development Helps the body in utilization of energy from food 	

Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Pyridoxine (Vitamin B6)	<ul style="list-style-type: none"> • A factor in maintenance of good health 	<ul style="list-style-type: none"> • Helps the body to metabolize proteins, fats and carbohydrates 	
Cyanocobalamine (Vitamin B12)	<ul style="list-style-type: none"> • Helps in maintenance of good health 	<ul style="list-style-type: none"> • Helps in the formation of red blood cell 	
Folic Acid		<ul style="list-style-type: none"> • Helps in formation of red blood cell 	<ul style="list-style-type: none"> • Helps prevent neural tube defects for women who are planning a pregnancy before conception and during 12 weeks of pregnancy at a dose of 400 mcg daily
Biotin	<ul style="list-style-type: none"> • Helps in maintenance of good health 	<ul style="list-style-type: none"> • Helps to metabolize fats and carbohydrates 	
Panthenic Acid	<ul style="list-style-type: none"> • Helps in maintenance of good health 	<ul style="list-style-type: none"> • Helps to metabolize fats and carbohydrates 	

Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Calcium	<ul style="list-style-type: none"> Helps in maintenance of good health 	<ul style="list-style-type: none"> Helps in the formation and maintenance of bones and teeth Claim for specific subgroup: <ul style="list-style-type: none"> Additional calcium is required for pregnant and lactating women, when diet does not provide a sufficient daily intake to help in proper bone formation in developing baby 	
Phosphorus	<ul style="list-style-type: none"> Helps in maintenance of good health 	<ul style="list-style-type: none"> Helps in the formation and maintenance of bones and teeth 	
Magnesium	<ul style="list-style-type: none"> Helps in maintenance of good health 	<ul style="list-style-type: none"> Helps the body to metabolize carbohydrate 	
Iron	<ul style="list-style-type: none"> Helps in maintenance of good health 	<ul style="list-style-type: none"> Helps in the formation of red blood cell 	<ul style="list-style-type: none"> Helps to prevent iron anemia Helps to prevent anemia due to iron deficiency
Iodine	<ul style="list-style-type: none"> Helps in maintenance of good health 	<ul style="list-style-type: none"> Helps in the function of the thyroid glands 	

Ingredients	Claims		
	General	Functional	Reduced Risk Reduction Claim
Zinc	<ul style="list-style-type: none"> A factor in maintenance of good health 	<ul style="list-style-type: none"> Helps to metabolize carbohydrates, fats and protein 	
Copper	<ul style="list-style-type: none"> A factor in maintenance of good health 	<ul style="list-style-type: none"> Helps in the formation of red blood cell 	
Manganese	<ul style="list-style-type: none"> A factor in maintenance of good health 	<ul style="list-style-type: none"> Helps to metabolize carbohydrates and proteins 	
Probiotics		<ul style="list-style-type: none"> Helps to improve a beneficial intestinal microflora 	

Notes:

1. This list is not meant to be exhaustive and will be reviewed from time to time.
2. The Authority will nonetheless conduct a detailed evaluation of the evidence included in the report to ensure that the health claim is substantiated.
3. The Authority will be willing to consider review other than the listed above, if the standards of evidence are consistent with those of the Authority.
4. All references must be current.

ACKNOWLEDGEMENTS

The National Pharmaceutical Control Bureau acknowledges its indebtedness to the members from the industries, government agencies and universities as stated below, who provided comments and advices during the preparation of these guidelines.

Government agencies:

- i) *Bahagian Keselamatan dan Kualiti Makanan (BKMM), KKM*
- ii) *Bahagian Perubatan Tradisional & Komplementari, KKM*
- iii) *Institut Penyelidikan dan Perubatan (IMR), KKM*
- iv) *Kementerian Pertanian & Industri Asas Tani Malaysia*
- v) *Unit Perancang Ekonomi, Jabatan Perdana Menteri*

Universities:

- i) *Jabatan Pemakanan dan Dietetik, Fakulti Perubatan & Sains Kesihatan, Universiti Putra Malaysia*
- ii) *Jabatan Pemakanan dan Dietetik, Fakulti Sains Kesihatan Bersekutu, Universiti Kebangsaan Malaysia*
- iii) *Pejabat Dietetik, Pusat Perubatan Universiti Malaya*
- iv) *Program Sains Makanan, Fakulti Sains dan Teknologi, Universiti Kebangsaan Malaysia*

Industries/ Associations:

- i) *Biotropic Malaysia Berhad*
- ii) *Direct Selling Association of Malaysia (DSAM)*
- iii) *Federation of Chinese Physician and Medicine-Dealers Association of Malaysia (FCPMDAM)*
- iv) *Malaysian Biotechnology Corporation (BiotechCorp)*
- v) *Malaysian Dietary Supplement Association (MADSA)*
- vi) *Malaysian Direct Distribution Association (MDDA)*
- vii) *Persatuan Industri Farmaseutikal Malaysia (MOPI)*
- viii) *Persatuan Pengeluar-pengeluar Ubat Tradisional Melayu Malaysia (PURBATAMA)*
- ix) *Perubatan Traditional India Malaysia (PEPTIM)*
- x) *Pharmaceutical Association of Malaysia (PhAMA)*

APPENDIX 5:

GUIDELINE ON REGISTRATION OF NATURAL PRODUCTS

IMPORTANT NOTES:

1. This document shall be read in conjunction with the relevant sections of the main DRGD.
2. Natural products will be evaluated based on the criteria for safety and quality of the product and where appropriate efficacy/ claimed benefits.
3. This document is intended to provide guidance for the registration of natural products. However, the document will serve as a living document that will be updated/ revised further in the line with the progress in scientific knowledge and experience.
4. The following lists are by no means exhaustive. It may be reviewed as and when it is deemed necessary.

Outline:

1. General Information

1.1 Definitions

1.1.1 Traditional Medicines

1.1.2 Finished Herbal Product

1.1.3 Herbal Remedy

1.1.4 Homeopathic Medicine

1.2 Exemption from Product Registration

1.3 Preparations which are not allowed to be registered

1.4 Classification for Specific Active Ingredients

1.4.1 Products Containing Cassia/ Senna

1.4.2 Products Containing Psyllium Husk/ Plantago Ovata

2. General Requirements for Registration of Natural Products

2.1 Ingredients

2.1.1 Active Ingredients

2.1.2 Premix

2.1.3 Prohibited/ Banned Ingredients

2.1.4 Use of Protected/ Endangered Ingredients

2.2 Excipients

2.3 Indications

2.3.1 Indications Acceptable for Natural Products

2.3.2 Non-Permissible Indications

2.4 Product Name

2.5 Quality Control

2.5.1 Sample for Testing

2.5.2 Appeal for Sample Retesting

2.5.3 Quality Testing for Specific Ingredient

2.5.4 Limit Test for Heavy Metals

2.5.5 Disintegration Test

2.5.6 Test for Uniformity of Weight (For Tablets and Capsules Only)

2.5.7 Tests for Microbial Contamination

2.6 Stability Data

2.7 Labelling Requirement

2.7.1 Statements to be stated on Product Label

2.7.2 Specific Labelling Statements/ Warning & Precautions

2.7.3 Cautionary Statement for Products Specially Used in Women

2.7.4 Prohibited Visual/ Graphics/ Statement on Label of Natural Products in Women

3. Product Specific Requirements:

3.1 Foot Patch

3.2 Herbal Tea

3.3 Homeopathic Products

1. GENERAL INFORMATION

1.1 DEFINITIONS

1.1.1 Traditional medicine

As defined under the CDCR 1984, traditional medicine refers to any product used in the practice of indigenous medicine, in which the drug consist solely of one or more naturally occurring substances of a plant, animal or mineral, of parts thereof, in the unextracted or crude extract form, and a homeopathic medicine. It shall not include any sterile preparation, vaccines, any substance derived human parts, any isolated and characterized chemical substances.

1.1.2 Finished Herbal Product

Finished herbal products consist of herbal preparations made from one or more herbs. If more than one herb is used, the term “mixture herbal product” can also be used. Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substance have been added, including synthetic compounds and/ isolated constituents from herbal materials, are not considered to be herbal.

1.1.3 Herbal Remedy

Any drug consisting of a substance or a mixture of substances produced by drying, crushing or comminuting, but without subjecting to any other process, a natural substance or substances of plant, animal or mineral origin, or any part of such substance or substances.

1.1.4 Homeopathic Medicine

Any pharmaceutical dosage form used in the homeopathic therapeutic system in which diseases are treated by the use of minute amounts as of such substances which are capable of producing in healthy persons symptoms similar to those of the disease being treated.

1.2 EXEMPTION FROM PRODUCT REGISTRATION

The following preparations do not require registration with the Authority:

- a) Extemporaneous preparation that has been prepared and given directly to the patient by any traditional practitioner during the course of treatment;
- b) Traditional preparation containing plants, animal parts or mineral substance or a mixture of these substances of natural origin that is produced only through drying, without any treatment/process involved. For example, raw herbs;
- c) Traditional preparation containing plants, animal parts, mineral substance/ extracts or a mixture of these substances of natural origin traditionally used as food, spices or flavouring of food which do not have any medicinal claim;
- d) Traditional preparation that is used for cosmetic purposes such as to whiten or improve the appearance of skin, hair, teeth, etc has to be registered as cosmetic product.

1.3 PREPARATIONS WHICH ARE NOT ALLOWED TO BE REGISTERED

- a) Traditional preparation with the indication as listed in “List of Non Permissible Indications for Natural Product”
(*Reference: Medicine Advertisement and Sale Act 1956*)
- b) Traditional preparation containing herbal ingredients as listed under Poison Act 1952 except for those exempted for homeopathic preparation. Please refer to Section 4 - General guidelines for the registration of homeopathic products.
- c) Traditional preparation containing ingredient known or reported to cause any adverse effect on humans. Please refer to List of Botanicals (& botanical ingredients) which are banned due to reported adverse event.
- d) Traditional preparation containing combination of plants, animal parts or mineral substance of natural origin with chemical/ synthetic substance with therapeutic effect.
- e) Traditional preparation containing combination of plants, animal parts or mineral substance of natural origin with vitamins and amino acids.

- f) Traditional products are prohibited from containing ingredients derived from human origin. For examples:
 - i) CRINIS CARBONISATUS = Carbonised human hair
(Reference: *Pharmacopoeia Of The People's Republic Of China: English Edition 1992*)
 - ii) HUMAN PLACENTA

1.4 CLASSIFICATION FOR SPECIFIC ACTIVE INGREDIENTS

1.4.1 PRODUCTS CONTAINING CASSIA/ SENNA:

Products containing less than 0.5g of the crude drug or 20 mg sennoside (standardized preparation) are allowed make claims for general health only.

(Reference: *Micromedex*)

1.4.2 PRODUCTS CONTAINING PSYLLIUM HUSK/ PLANTAGO OVATA

Finished products containing less than 3.5g of this active ingredient in a single formulation and not in a pharmaceutical dosage form with specific dosage instructions will be classified as a non-drug. However quantities above this amount and up to 6.9 g will require this product to be classified as a traditional product and will require registration before it can be marketed.

(Reference: Circular on 14 May 2010 - [Bil \(24\) dlm.BPFI/PPP/07/11Jld 5](#))

2. GENERAL REQUIREMENTS FOR REGISTRATION OF NATURAL PRODUCTS

2.1 INGREDIENTS

2.1.1 ACTIVE INGREDIENTS

- a) Active ingredients are those substances that have a therapeutic role in the formulation. Substances that are included in the formulation as active ingredients must make a contribution to the proposed indications for the product. Where a claim links the presence of an ingredient to the product

indication, that ingredient must contribute to that indication. The evidence may be scientific and or traditional.

- b) Overages of active ingredient
Overages may be used during manufacture. An overage is where the amount of an ingredient added during manufacturing that is greater than the nominated on the product label. Details of the overage used must be available
- c) Listed active ingredients can be checked through <http://www.bpfk.gov.my> of product search. Ingredients not listed will require safety and/or efficacy data evaluation prior to addition to this list.
- d) For new active ingredients or new combination products, the following information shall be required:
 - Product containing new single ingredient:
 - i) **Extract form**
 - Information on the taxonomy of the ingredient;
 - Techniques and methods in preparing/ processing the extract and subsequently the product;
 - Information on the use and safety of the ingredient and the product Quality standard.
 - ii) **Powder/ Granules**
 - Information on the taxonomy of the ingredient;
 - Techniques and methods in preparing/ processing the extract and subsequently the product;
 - Information on the use and safety of the ingredient and the product.
 - Product containing multiple ingredients (contains ingredients which are known to be used traditionally):
 - The source of the product formulation;
e.g. Chinese Pharmacopoeia
 - Proof or evidence of the use, traditionally.

- Product containing multiple ingredients (contains ingredients which are not known to be used traditionally):
 - Information on the use and safety of every new ingredient;
 - Safety data on the new formulation;
 - Regulatory status in other countries.

2.1.2 PREMIX

Effective from 1 December 2007, premixed ingredient(s) shall not be used in a traditional product formulation, as directed in circular [Bil \(71\) dlm BPFK/02/5/1.3](#), 1 Jun 2007

2.1.3 PROHIBITED/ BANNED INGREDIENTS

The following lists are prohibited/ banned ingredients which are not allowed in the formulation of natural products registered by the Authority:

- a) Botanicals (and botanical ingredients) containing scheduled poisons as listed under the Poisons Act 1952;
- b) Botanicals (& botanical ingredients) which are banned due to reported adverse event;
- c) Ingredients (botanicals and substance derived from animals) which are banned due to safety reasons.

a) Table 1: Botanicals (and botanical ingredients) containing scheduled poisons as listed under the Poisons Act 1952

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
<i>Aconitum</i>	All species			Aconite
<i>Asidosperma</i>	<i>quebracho</i>	White quebracho		Asidospermine, yohimbine
<i>Atropa</i>	<i>belladonna</i>	Deadly nightshade		Atropine, hyoscyamine (scopolamine), hyoscyamine
<i>Berberis</i>	All species			Berberine * Also present in <i>Hydrastis canadensis</i> (Goldenseal) and <i>Coptis chinensis</i> (Golden thread)
<i>Cabola</i>	<i>albarrane</i>	Squill		Glycoside
<i>Catharanthus</i>	<i>roseus</i>	Periwinkle Madagascar, Old Maid, <i>Vinca rosea</i> , Myrtle Syn: <i>Vinca balcanica</i> , <i>Vinca difformis</i> , <i>Vinca heracea</i> , <i>Vinca major</i> , <i>Vinca minor</i> , <i>Vincae minoris</i> herba		Vinca, Vincristine, Vinblastine

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
<i>Chondodendron</i>	<i>tomentosum</i>	Curare, Velvet leaf, Ice Vine,		Tubocurarine
<i>Claviceps</i>	<i>purpurea</i>	Ergot		Ergometrine
<i>Colchicum</i>	<i>autumnale</i>	Autumn Crocus/ Meadow Saffron/ Naked Lady)		Colchicine
<i>Datura</i>	<i>metel</i>	Devil's Trumpet, Metel, J California Jimson Weed Syn.: <i>Datura wrightii</i>		Atropine, Scopolamine
<i>Datura</i>	<i>stramonium</i>	Jimson Weed/ Gypsum Weed, Loco Weed		Atropine, Hyoscyamine, Scopolamine
<i>Delphinium</i>	<i>staphysagria</i>	Lice bane, Stavesacre		Delphinine
<i>Digitalis</i>	<i>purpurea</i>	Common Foxglove, Purple Foxglove, Kecubung	Leaf	Glycoside
<i>Drimia</i>	<i>maritima</i>	Squill Syn.: <i>Urginea maritima</i> , <i>Scilla maritima</i>		Glycoside

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
		Related substance: <i>Urginea indica</i> , <i>Urginea pancreatium</i> , <i>Urginea scilla</i>		
<i>Ephedra</i>	All species	Ma Huang		Ephedrine, Pseudoephedrine
<i>Gelsemium</i>	<i>sempervirens</i>	Yellow Jessamine, Eve ning Trumpet, Caroli na Jessamine		Gelsemine
<i>Hyoscyamus</i>	<i>muticus</i>	Egyptian henbane		Hyoscyamine
<i>Hyoscyamus</i>	<i>niger</i>	Black henbane		Hyoscyamine- atropine
<i>Lobelia</i>	<i>inflata</i>	Lobelia, pokeweed, Indian tobacco, gagroot, asthma weed, vomitwort, bladderpod, rap untium inflatum.		Lobeline
<i>Lobelia</i>	<i>nicotianifolia</i>	Wild Tobacco		Lobeline
<i>Mitragyna</i>	<i>speciosa</i>	Daun Ketum		Mitrogynine
<i>Nicotiana</i>	<i>tabacum</i>	Common tobacco		Nicotine

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
<i>Papaver</i>	<i>somniferum</i>	Opium poppy		Morphine, codeine, hydrocodone, meperidine, methadone, papaverine
<i>Pausinystalia</i>	<i>yohimbe</i>	Yohimbe, Johimbe Syn. <i>Corynanthe johimbi</i> , <i>Coryna nthe yohimbi</i>		Yohimbine
<i>Physostigma</i>	<i>venenosum</i>	Calabar bean		Physostigmine
<i>Pilocarpus</i>	<i>microphyllus</i>	Pilocarpus jaborandi, jaborandi		Pilocarpine
<i>Punica</i>	<i>granatum</i>	Pomegranate	Bark	Iso-Pellatrierine
<i>Rauwolfia</i>	<i>serpentina</i>	Indian snakeroot, Serpentine root		Reserpine
<i>Rauwolfia</i>	<i>vomitoria</i>	African serpentwood		Reserpine
<i>Schoenocaulon</i>	<i>officinale</i>	Veratrum officinale		Sabadilla, Veratrine
<i>Scillae</i>	<i>bulbus</i>	Sea onion, Squill		
<i>Solanum</i>	<i>nigrum</i>	Black nightshade		Solanine

Genus	Species	Common/ Local Name	Part of plant prohibited (whole plant unless otherwise specified)	Constituent(s) of concern
<i>Strychnos</i>	<i>nux-vomica</i>	Poison nut, Quaker button, strychnine tree, ma qian zi/maqianzi		Strychnine
<i>Valerian</i>	All species		All parts except for root part	Valepotriates
<i>Veratrum</i>	All species			
<i>Vinca</i>	All species	Including <i>Catharanthus</i> <i>roseus</i>		Vinca, Vincristine, Vinblastine, Vinpocetin

b) Table 2: Botanicals (& botanical ingredients) which are banned due to reported adverse event

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
Aristolochia	All species			Contain Aristolochic Acid reported to cause kidney toxicity (**Please refer to footnote below)
Drybalanops	aromatica	Borneo /Malay/Sumatra Camphor, Pokok Kapur	Whole herb	Contain camphor- not allowed for oral preparation
Borneolum	syntheticum	Bingpian, borneol		Contain borneol- not allowed for oral preparation
Larrea	tridenata	Chapparral		Reported to cause liver toxicity
	mexicana			
Hydrastis	canadensis	Goldenseal, Eye Balm, Indian Dye		Reported to cause disturbance of the nervous system
Magnolia	officinalis	Houpu, Magnolia		Reported to cause kidney toxicity
Stephania	tetrandra			
Piper methysticum		Kava-kava		Reported to cause liver toxicity
Symphytum	officinale	Comfrey		
	asperum			
	x. uplandicum			

Genus	Species	Common/ Local Name	Part of plant prohibited	Reason for prohibition
Senecio	aureus	Life root		Reported to cause liver toxicity
	jacobaea	Tansy ragwort, Tansy Butterweed		
	bicolor	Silver ragwort		
	nemorensis	Alpane ragwort, Wood ragwort		
	vulgaris	Common groundsel, Groundsel, Old-man-in the-spring		
	longilobus -syn .with douglasii, filifolius	Threadleaf groundsel, Threadleaf ragwort		
	Scandens Buch.-Ham	German/African/ Cape Ivy, Climbing Groundsel		

****** To identify the Botanicals which may contain Aristolochic Acid besides the Aristolochia genus, please refer the following lists on the next page:

- a. List A - Botanicals Known or Suspected to contain Aristolochic Acid**
- b. List B - Botanicals which may be Adulterated with Aristolochic Acid**

Notes:

Products containing any of the listed herbs (EXCEPT for Aristolochia spp. which is totally banned) will have to be sent to any governmental doping centre for testing and the result shall be attached with the registration form.

(Source for Lists A and B)

U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Nutritional Products, Labeling, and
Health Supplements
[Revised April 9, 2001]

List A: Botanicals Known or Suspected to Contain Aristolochic Acid**Table 3:**

Botanical Name*	Common or Other Names
Asarum canadense Linn. Syn. Asarum acuminatum (Ashe) E.P. Bicknell Syn. Asarum ambiguum (E.P. Bicknell) Daniels Syn. Asarum canadense var. ambiguum (E.P. Bicknell) Farw. Syn. Asarum canadense var. reflexum (E.P. Bicknell) B.L. Rob. Syn. Asarum furcatum Raf. Syn. Asarum medium Raf. Syn. Asarum parvifolium Raf. Syn. Asarum reflexum E.P. Bicknell Syn. Asarum rubrocinctum Peattie	Wild ginger Indian ginger Canada snakeroot False coltsfoot Colic root Heart snakeroot Vermont snakeroot Southern snakeroot
Asarum himalaicum Hook. f. & Thomson ex Klotzsch or Asarum himalaycum Hook. f. & Thomson ex Klotzsch	Tanyou-saishin (Japanese)
Asarum splendens (F. Maek.) C.Y. Cheng & C.S. Yang	Do-saishin (Japanese)
Bragantia wallichii R.Br. Specimen exists at New York Botanical Gardens.	

Botanical Name*	Common or Other Names
<p>Tropicos</p> <p>does not list this species as a synonym for any Thottea</p> <p>species. Kew Gardens Herbarium does not recognize the</p> <p>genera Bragantia. Until additional information is obtained we</p> <p>will use the name as cited in J. Nat. Products 45:657-666</p> <p>(1982)</p>	

List B: Botanicals which may be Adulterated with Aristolochic Acid**Table 4:**

Botanical Name*	Common or Other Names
Akebia spp.	<p>Akebia</p> <p>Mu tong</p> <p>Ku mu tong</p> <p>Zi mutong</p> <p>Bai mu tong</p> <p>Mokutsu (Japanese)</p> <p>Mokt'ong (Korean)</p>
<p>Akebia quinata (Houtt.) Decne.</p> <p>Syn. Rajania quinata Houtt.</p>	<p>Chocolate vine</p> <p>Fiveleaf akebia</p> <p>Mu tong</p> <p>Yu zhi zi</p> <p>Mokutsu (Japanese)</p>

Botanical Name*	Common or Other Names
Akebia trifoliata (Thunb.) Koidz.	Mu tong Three leaf akebia Yu zhi zi
Asarum forbesii Maxim.	Batei-saishin (Japanese)
Asarum heterotropoides F. Schmidt Syn. Asarum heterotropoides F. Schmidt Syn. Asiasarum heterotropoides (F. Schmidt) F. Maek.	Keirin-saishin (Japanese) Chinese wild ginger Manchurian wild ginger Bei xi xin Xin xin
Asarum sieboldii Miq. Syn. Asarum sieboldii fo. seoulense (Nakai) C.Y. Cheng & C.S. Yang Syn. Asarum sieboldii var. seoulensis Nakai Syn. Asiasarum heterotropoides var. seoulense (Nakai) F. Maek. Syn. Asiasarum sieboldii (Miq.) F. Maek.	Usuba-saishin (Japanese) Chinese wild ginger Xi Xin Hua Xi Xin Manchurian wild ginger Siebold's wild ginger
Clematis spp.	Clematis Mufangji Clematidis Ireisen (Japanese) Wojoksum (Korean)

Botanical Name*	Common or Other Names
<p>Clematis armandii Franch.</p> <p>Syn. Clematis armandii fo. farquhariana (W.T. Wang)</p> <p>Rehder & E.H. Wilson</p> <p>Syn. Clematis armandii var. biondiana (Pavol.) Rehder</p> <p>Syn. Clematis biondiana Pavol.</p> <p>Syn. Clematis ornithopus Ulbr.</p>	<p>Armand's clematis</p> <p>Chuan mu tong (stem)</p> <p>Xiao mu tong</p> <p>Armand's virgin bower</p>
<p>Clematis chinensis Osbeck.</p>	<p>Chinese clematis</p> <p>Wei ling xian (root)</p>
<p>Clematis hexapetala Pall.</p>	
<p>Clematis montana Buch.-Ham. ex DC.</p> <p>Syn. Clematis insulari-alpina Hayata</p>	
<p>Clematis uncinata Champ. ex Benth.</p> <p>Syn. Clematis alsomitriifolia Hayata</p> <p>Syn. Clematis chinensis var. uncinata (Champ. ex Benth.) Kuntze</p> <p>Syn. Clematis drakeana H. Lév. & Vaniot</p> <p>Syn. Clematis floribunda (Hayata) Yamam.</p> <p>Syn. Clematis gagnepainiana H. Lév. & Vaniot</p> <p>Syn. Clematis leiocarpa Oliv.</p> <p>Syn. Clematis ovatifolia T. Ito ex Maxim.</p> <p>Syn. Clematis uncinata var. biternata W.T. Wang</p> <p>Syn. Clematis uncinata var. coriacea Pamp.</p> <p>Syn. Clematis uncinata var. floribunda Hayata</p> <p>Syn. Clematis uncinata var. ovatifolia (T. Ito ex Maxim.)</p> <p>Ohwi ex Tamura</p> <p>Syn. Clematis uncinata var. taitongensis Y.C. Liu & C.H. Ou</p>	

Botanical Name*	Common or Other Names
Cocculus spp.	Cocculus
Cocculus carolinus (L.) DC. Syn. Cebatha carolina Britton Syn. Epibaterium carolinum (L.) Britton Syn. Menispermum carolinum L.	
Cocculus diversifolius DC. Syn. Cocculus madagascariensis Diels	
Cocculus hirsutus (L.) Diels Syn. Cocculus villosus DC. Syn. Menispermum hirsutum L.	
Cocculus indicus Royle Syn. Anamirta paniculata Colebr.	Indian cockle
Cocculus laurifolius DC. Syn. Cinnamomum esquirolii H. Lév.	
Cocculus leaebe DC.	
Cocculus madagascariensis Diels Syn. Cocculus diversifolius DC.	
Cocculus orbiculatus DC. Syn. Cissampelos pareira Linn. Cocculus orbiculatus (L.) DC. Syn. Cocculus cuneatus Benth. Syn. Cocculus sarmentosus (Lour.) Diels Syn. Cocculus sarmentosus var. linearis Yamam. Syn. Cocculus sarmentosus var. pauciflorus Y.C. Wu Syn. Cocculus sarmentosus var. stenophyllus Merr. Syn. Cocculus thunbergii DC.	Moku-boui (Japanese)

Botanical Name*	Common or Other Names
Syn. Cocculus trilobus (Thunb.) DC. Syn. Menispermum orbiculatus L. Syn. Menispermum trilobum Thunb. Syn. Nephroia sarmentosa Lour.	
Cocculus palmatus (Lam.) DC.	Columba Columbo
Cocculus pendulus Diels Syn. Cebatha pendula (J.R. & C. Forst.) Kuntze Syn. Epibaterium pendulus Forst. f. Syn. Cocculus Epibaterium DC.	
Cocculus pendulus (Forst. & Forst.) Diels	
Cocculus palmatus Hook. Syn. Jateorhiza Miersii Oliver	Colombo
Cocculus thunbergii DC.	
Diploclisia affinis (Oliv.) Diels Syn. Diploclisia chinensis Merr. Syn. Cocculus affinis Oliv.	
Diploclisia chinensis Merrill	Xiangfangchi
Menispermum dauricum	
Saussurea lappa (Decne.) Sch. Bip. / Aucklandia Lappa	Mokkou (Japanese)

Botanical Name*	Common or Other Names
<p>Sinomenium acutum (Thunb.) Rehder & E.H. Wilson</p> <p>Syn. Cocculus diversifolius var. cinereus Diels</p> <p>Syn. Cocculus heterophyllus Hemsl. & E.H. Wilson</p> <p>Syn. Menispermum acutum Thunb.</p> <p>Syn. Sinomenium acutum (Thunb.) Rehder & E.H. Wilson</p> <p>var. cinereum (Diels) Rehder & E.H. Wilson</p> <p>Syn. Sinomenium diversifolium (Diels) Diels</p>	<p>Orientvine</p> <p>Xunfengteng</p> <p>Dafengteng</p> <p>Daqingmuxinag</p> <p>Zhuigusan</p> <p>Da ye qingshener</p> <p>Mufangji</p> <p>Hanfangji</p> <p>Tuteng</p> <p>Zhuigufeng</p> <p>Maofangji</p>
Stephania spp.	Stephania
<p>Stephania tetrandra S. Moore</p> <p>Vladimiria souliei (Franch.) Ling</p>	<p>Fen fang ji , fang ji</p> <p>Fang ji (root)</p> <p>Han fang ji</p> <p>Kanboi (Japanese)</p> <p>Hanbanggi (Korean)</p> <p>Fun-boui (Japanese)</p> <p>Sen-mokkou</p>

c) Ingredients (Botanicals and Substance Derived from Animals) which are banned due to safety reasons:

Table 5:

Genus	Species	Part of Plant/ Animal Prohibited (whole plant/ animal unless otherwise specified)	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
<i>Abrus</i>	<i>precatorius</i>	Seed	Abrin, Agrus, Agglutinin	<ul style="list-style-type: none"> - Potent inhibitor of protein and DNA synthesis - Severe diarrhea - Severe stomach cramp - Severe gastroenteritis
<i>Adonis</i>	<i>vernalis</i>		Adonitoxin	Uncontrolled dose can damage heart and cause death
Animal parts containing hormones (All species)				
<i>Antiaris</i>	<i>toxicaria</i>	Latex, sap	Cardiac glycoside (antiarin), Cardenolides & alkaloids with cardiac arresting potential	<ul style="list-style-type: none"> - Latex is highly poisonous - Paralyze heart muscle and cause death
<i>Aristolochia</i>	<i>All species</i>		Aristolochic acid	Reported to cause kidney toxicity, interstitial nephropathy
<i>Calotropis</i>	<i>gigantean</i>	Latex	Cardiac glycosides, calotropin	Severe mucous membrane irritation characterized by vomiting, diarrhea, bradycardia, convulsion and death
	<i>procera</i>			

Genus	Species	Part of Plant/ Animal Prohibited (whole plant/ animal unless otherwise specified)	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
<i>Cannabis</i>	<i>sativa</i>		Cannabinoids	<ul style="list-style-type: none"> - Potential abuse - Psychoactive on CNS - Prolonged heavy use may lead to tolerance and psychological dependence
	<i>indica</i>			
<i>Catharanthus</i>	<i>roseus</i>		Vinca alkaloids	Bone marrow depression, central and peripheral (including autonomic) neurotoxicity
<i>Cerbera</i>	<i>manghas</i>	Seed	Digitoxinglycoside, Cerberine, Cerberoside, thevetin	<ul style="list-style-type: none"> - Drastic purgative and emetic - Burning in the stomach sensation, vertigo, nausea, violent purgation and colic - Heart failure
	<i>odollam</i>	Seed	Cerberine, Cerberoside, odollin, odolotoxin, thevetin and cerapain	<ul style="list-style-type: none"> - Gastro intestinal symptoms - cardiac toxicity - Nausea, severe retching, vomiting, abdominal pain, blurring of vision - Arterial block and nodal rhythm, hyperkalaemia - Irregular respiration, collapse and death from heart failure
<i>Cinchona</i>	<i>All species</i>		Quinine and derivatives	<ul style="list-style-type: none"> - Resistance of malarial vector - Use of bark is contraindicated in pregnancy and ulcers, intestinal or gastric, and if taken concomitantly with anticoagulants can increased

Genus	Species	Part of Plant/ Animal Prohibited (whole plant/ animal unless otherwise specified)	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
				<p>their effects</p> <ul style="list-style-type: none"> - Can elicit thrombocytopenia with purpura - Cinchona alkaloids are toxic. Can cause symptoms such as blindness, deafness, convulsions and paralysis
<i>Citrullus</i>	<i>Colocynthis</i>	Seed, fructus	Curcubitacin	<ul style="list-style-type: none"> - Carcinogenic effects, induce infertility in both sexes - Enterohepatonephro-toxicity
<i>Dryopteris</i>	<i>filix-mas</i>	Rhizome	Filicin, aspidinol	Hepatotoxic and blindness
<i>Euphorbia</i>	<i>antiquorum</i>	Latex	Apha euphorbol, Beta amyrin cycloartenol Euphol	Inflammation of the gastrointestinal mucous membrane, irritate skin, difficult respiration, eyes pupil dilated
	<i>trigona</i>			
<i>Excoecaria</i>	<i>agallocha</i>	Latex	Excoecaria phorbol	<ul style="list-style-type: none"> - Highly irritant to skin - Cause blindness if it enters the eye - Biocidal
<i>Garcinia</i>	<i>acuminate</i>	Gum resin	Cambogic acid, β -guttiferin, α -1 guttiferin	Vomiting, hypercarthasis, sympathetic irritation of sympathetic nervous system, caused death by gastro-enteritis
	<i>hanburyi</i>			
	<i>morella</i>			
<i>Gelsemium</i>	<i>elegans</i>	Root, leaf, rhizome	Gelsemine & gelseminine (Gelsemium indole alkaloid)	Paralysis, shortness of breath, muscle stiffeningcoma, hypocyclosis

Genus	Species	Part of Plant/ Animal Prohibited (whole plant/ animal unless otherwise specified)	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
<i>Hyoscyamus</i>	<i>muticus</i>		Hyoscyamine, atropine, hyoscine	Difficulty in swallowing and talking, transient bradycardia followed by tachycardia with palpitation and arrhythmias, CNS depression, coma
<i>Jatropha</i>	<i>multifida</i>	Fruit, seed	Phytotoxin (toxalbumin - Curcin	Nausea, vomiting, serious purgative action
<i>Lantana</i>	<i>camara</i>		Lantadene, Lancamaron	Cause toxicity in buffalo, cattle, sheep and goat. Symptoms include photosensitive dermatitis, jaundice and yellowing of mucous membrane and loss of appetite with a decrease in ruminal motility
<i>Lobelia</i>	<i>chinensis</i>		Lobeline	- Stimulant and has peripheral and central effects - Excessive use can cause nausea, vomiting and dizziness
	<i>tupa</i>			- Stimulant and has peripheral and central effects - Caused arrhythmias
<i>Lytta</i>	<i>vesicatoria</i>	Whole body, tincture	Cantharidin	- Excessive salivation, abdominal pain, swelling of kidney and urogenital system, headache, vomiting and diarrhea accompanied by bleeding - Burning of the mouth, dysphagia, nausea, hematemesis, gross hematuria and dysuria

Genus	Species	Part of Plant/ Animal Prohibited (whole plant/ animal unless otherwise specified)	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
				- Renal dysfunction and related to acute tubular necrosis and glomerular destruction
<i>Melaleuca</i>	<i>alternifolia</i>		Tea tree oil	Skin irritation, respiratory distress, vomiting, diarrhea and cytotoxic for oral administration. * Banned in oral preparation
<i>Papaver</i>	<i>All species</i>		Morphine and derivatives, codeine	- Potential abuse - Dependence, palpitation, hallucination, euphoric activities, CNS depression - Nervous system toxicity - Possible death from circulatory and respiratory failure
<i>Pilocarpus</i>	<i>pinnatifolius</i>	Bark	Pilocarpine	Bronchospasm, ocular problem, miosis, blurred vision
	<i>jaborandi</i>			
<i>Podophyllum</i>	<i>emodii</i>	Root, leaf	Podophyllin resin	- Serious systemic toxicity with excessive amounts (persistent nausea and vomiting, tachypnea, fever, stupor, coma, tachycardia, neuropathy and death) - Renal failure and hepatotoxicity
	<i>peltatum</i>			
<i>Solanum</i>	<i>dulcamara</i>	Leaf, flowering tops	Solanaceous alkaloids	Typical antimuscarinic effect e.g. dry mouth, mydriasis

Genus	Species	Part of Plant/ Animal Prohibited (whole plant/ animal unless otherwise specified)	Constituent of Concern Reasons for Prohibition	Reasons for Prohibition
<i>Strophantus</i>	<i>All species</i>		Strophantus alkaloids	Cardiac effect similar to digoxin
<i>Symphytum</i>	<i>pregrinum</i>		Pyrrolizidine alkaloid	Reported to cause liver toxicity

2.1.4 USE OF PROTECTED/ ENDANGERED INGREDIENTS

a) PROTECTED/ ENDANGERED WILDLIFE SPECIES

It is the responsibility of the applicant to ensure that the ingredient(s) derived from wildlife species its parts and derivatives used in the formulation **COMPLIES** with the Wildlife Conservation Act 2010 (Act 716) and International Trade in Endangered Species Act 2008 (Act 686). Both guidelines can be downloaded through this link <http://www.wildlife.gov.my>.

The applicant shall contact the following department to obtain the necessary permit/ license. A copy of the permit/ license shall be attached together with the application form for product registration.

Department of Wildlife and National Parks, Peninsular Malaysia
Km. 10, Jalan Cheras,
56100 Kuala Lumpur,
Tel: +603-90866800, Fax: +603-90753873

b) ENDANGERED BOTANICAL SPECIES

It is the responsibility of the applicant to declare the source of the botanical ingredient if it is listed under the International Trade in

Endangered Species Act 2008 (Act 686). If the ingredient is from a local source, a special permit/ license shall be obtained from the:

Division of Protection and Quarantine of Plants,
Department of Agriculture,
Tingkat 1-3, Wisma Tani,
Jalan Sultan Salahuddin,
50632 Kuala Lumpur.
Tel: +603 - 20301400, Fax: +603 - 26913550.

2.2 EXCIPIENTS

- a) Excipients are substances used to assist in the manufacture of active substance into dosage forms suitable for administration to consumers. Each excipient ingredient included in a formulation must have a justifiable excipient role and shall be controlled by specifications. The intended use of an excipient shall be appropriate.
- b) New excipient will require safety and/or other additional data to support the function in the product prior to addition into the Quest 3 database.
- c) LIST OF RESTRICTED EXCIPIENTS:

Specific Excipient	Limits (Not allowed)
1. Menthol	<ul style="list-style-type: none">- Oral (>10mg/day)- External (>10%)

2.3 INDICATIONS

2.3.1 INDICATIONS ACCEPTABLE FOR NATURAL PRODUCTS

a) General Health Maintenance/ *Kesihatan Am*

“Traditionally used..../ “*Digunakan secara tradisional....*

“Digunakan secara homeopati untuk.../ “*Homeopathically used....*

- 1. For general health/ for health/ *untuk kesihatan.*

2. General health maintenance/ for general well being.
3. For health and strengthening the body/ *untuk kesihatan dan menguatkan badan.*
4. For relief of body heatiness/ *untuk melegakan panas badan.*
5. For general debility, weakness after illness or childbirth/ *untuk letih lesu/ kelesuan badan selepas sakit atau selepas bersalin.*
6. For loss of appetite/ *untuk kurang selera makan.*
7. For difficulty in sleep/ *bagi melegakan kesukaran untuk tidur.*
8. For relief of fatigue/ *untuk melegakan kepenatan.*
9. As an aid to overcome fatigue during physical exertion/ *membantu melegakan kepenatan fizikal.*
10. To expel wind and invigorate vital energy/ *untuk membuang angin dan menambah tenaga.*
11. To improve appetite/ *untuk menambah selera makan.*
12. For relieving waist ache and body weakness/ *untuk melegakan sakit pinggang dan lemah anggota badan.*
13. For relieving dizziness, sweating, and difficulty in sleep/ *untuk melegakan pening, berpeluh berlebihan dan sukar untuk tidur.*
14. For reducing body odour/ *untuk mengurangkan bau badan.*
15. For reducing toothache/ *untuk mengurangkan sakit gigi.*
16. To relieve tired eyes/ *untuk melegakan kepenatan mata.*
17. For healthy eyes/ *untuk kesihatan mata.*

b) Blood & Body Fluid/ *Darah & Cecair Badan*

“Traditionally used..../ “*Digunakan secara tradisional....*

1. For improving blood circulation/ *untuk melancarkan perjalanan darah.*
2. To improve urination/ *untuk melawaskan kencing/ buang air kecil.*
3. For improving bowel movement/ *untuk melawaskan buang air besar.*
4. For relieving mild vomiting/ *untuk melegakan muntah ringan.*
5. For reducing minor swelling/ *untuk melegakan bengkak-bengkak ringan.*

c) Bone, Muscle & Joint/ *Tulang, Otot & Sendi*

“Traditionally used..../ “*Digunakan secara tradisional....*

1. For strengthening muscle and bone/ *untuk menguatkan otot dan tulang.*
2. For relieving muscular ache/ *untuk melegakan sakit otot.*

3. For relieving waist ache and backache/ *untuk melegakan sakit pinggang dan sakit belakang.*
4. For relief of joints and muscular pain/ *untuk melegakan sakit sendi dan otot.*
5. For relieving muscles sprain/ *untuk melegakan terseliuh/ terkehel.*

d) Pain & Fever/ Sakit Am & Demam

“Traditionally used..../ “*Digunakan secara tradisional....*

1. To relieve/ alleviate pain/ *untuk melegakan kesakitan.*
2. For relieving fever/ *untuk melegakan demam.*
3. For relieving headache/ *untuk melegakan sakit kepala.*
4. For relieving pain and itchiness related to piles/ *untuk melegakan kesakitan dan rasa gatal akibat buasir.*
5. For symptomatic relief of body heatiness/ body heat / *untuk melegakan panas badan.*

e) Cough & Cold/ Batuk & Selsema

“Traditionally used...../ “*Digunakan secara tradisional.....*

1. For relief of fever, cough and cold/ *untuk melegakan demam, batuk dan selsema.*
2. For relief of sore throat/ *untuk melegakan sakit tekak.*
3. For reducing phlegm and relief of cough, sore throat and body heatiness/ *untuk mengurangkan kahak dan melegakan batuk, sakit tekak dan panas badan.*
4. For relief of throat irritations and cough/ *untuk melegakan sakit tekak dan batuk.*
5. For relief of nasal congestion/ *untuk melegakan hidung tersumbat.*
6. For relief of sore throat and cough/ *untuk melegakan sakit tekak dan batuk.*
7. For relief of mouth ulcers due to heatiness/ *untuk melegakan sakit mulut akibat panas badan.*
8. To relieve sinusitis/ *untuk melegakan resdung.*

f) Digestive System/ Sistem Pencernaan

“Traditionally used..../ “*Digunakan secara tradisional....*

1. For relief of stomach ache, mild diarrhoea/ *untuk melegakan sakit perut, cirit-birit ringan.*
2. For relief of flatulence, stomach ache, mild diarrhoea, and loss of appetite/ *untuk melegakan kembung perut, sakit perut, cirit-birit ringan dan kurang selera makan.*
3. For relief of mild diarrhoea, vomiting and improve appetite/ *untuk melegakan cirit-birit, muntah ringan dan menambah selera makan.*
4. For relief of mild constipation/ *untuk melegakan sembelit ringan.*
5. To improve appetite and digestion/ *untuk menambah selera makan dan pencernaan.*
6. For relieving abdominal pain and flatulence/ *untuk melegakan sakit perut dan kembung perut.*
7. For relief of stomach ache, constipation, mild vomiting and indigestion/ *untuk melegakan sakit perut, sembelit, muntah ringan dan makanan tidak hadzam.*
8. Aid in digestion/ *untuk membantu penghadzaman.*

g) Women's Health/ Kesihatan Wanita

“Traditionally used...../ “*Digunakan secara tradisional....*

1. To relieve menstrual pain, headache and to regulate menstruation/ *untuk melegakan senggugut, sakit kepala dan melancarkan perjalanan haid.*
2. To reduce body weight/ *untuk mengurangkan berat badan.*
3. For relief of vaginal discharge/ *untuk melegakan keputihan.*
4. For women after childbirth/ *untuk wanita lepas bersalin.*
5. For general wellbeing and strengthen the body after childbirth/ *untuk kesihatan dan menguatkan badan wanita selepas bersalin.*
6. For women after childbirth to reduce body weight/ *untuk ibu-ibu selepas bersalin untuk mengurangkan berat badan.*
7. For symptomatic relief of vaginal discharge and mild itch/ *untuk melegakan keputihan dan gatal-gatal ringan.*
8. To improve menstrual flow, for relief of menstrual pain, vaginal discharge and flatulence/ *untuk melancarkan haid, melegakan senggugut, keputihan dan kembung perut.*

9. For strengthening body muscle and reducing body weight/ *untuk mengencangkan otot-otot tubuh dan mengurangi berat badan.*
10. For general health of women after childbirth/ *untuk menyihatkan rahim selepas melahirkan anak.*
11. To relieve symptoms of menopause/ *untuk melegakan simptom menopause. [Note: For specific active ingredient only, examples: red clover (trifolium pratense) and black cohosh (cimicifuga racemosa)]*

h) Men's Health/ Kesihatan Lelaki

“Traditionally used..../ “*Digunakan secara tradisional....*

1. For energy and men's health/ for vitality/ *untuk memulihkan tenaga dan kesihatan lelaki.*

i) Skin And External Usage/ Kulit Dan Kegunaan Luar

“Traditionally used...../ “*Digunakan secara tradisional...*

1. For symptomatic relief of pain and itch associated with insect bites/ *untuk melegakan sakit dan gatal-gatal digigit serangga.*
2. For relief of minor burns/ *untuk melegakan melecur ringan.*
3. For relief minor cuts/ *untuk melegakan luka-luka ringan.*
4. For relief of minor bruises/ *untuk melegakan lebam yang ringan.*
5. For reducing pimples/ *untuk mengurangkan jerawat.*
6. To help maintaining healthy skin, nail and hair/ *untuk kesihatan kulit, kuku dan rambut.*
7. For reducing pimples and mild itch/ *untuk melegakan jerawat dan gatal-gatal ringan.*

2.3.2 NON-PERMISSIBLE INDICATIONS

Table 6:

NO.	NON-PERMISSIBLE INDICATIONS
1.	<i>Penyakit atau kecacatan ginjal / Disease or defects of the kidney</i>

NO.	NON-PERMISSIBLE INDICATIONS
2.	<i>Penyakit atau kecacatan jantung / Disease or defects of the heart</i>
3.	<i>Kencing manis / Diabetes</i>
4.	<i>Epilepsi atau sawan / Epilepsy or fits</i>
5.	<i>Kelumpuhan / Paralysis</i>
6.	<i>Tibi / Tuberculosis</i>
7.	<i>Asma / Asthma</i>
8.	<i>Kusta / Leprosy</i>
9.	<i>Kanser / Cancer</i>
10.	<i>Kepekakan / Deafness</i>
11.	<i>Ketagihan dadah / Drug addiction</i>
12.	<i>Hernia atau pecah / Hernia or rupture</i>
13.	<i>Penyakit mata / Disease of the eye</i>
14.	<i>Hipertensi (Darah Tinggi) / Hypertension</i>
15.	<i>Sakit otak / Mental disorder</i>
16.	<i>Kemandulan / Infertility</i>
17.	<i>Kaku / Frigidity</i>
18.	<i>Lemah fungsi seks atau impoten / Impairment of sexual function or impotency</i>
19.	<i>Penyakit venerus / Venereal disease</i>
20.	<i>Lemah urat saraf atau aduan atau kelemahan lain timbul daripada atau perhubungan dengan perhubungan seks / Nervous debility or pother complaint of infirmity arising from or relating to sexual intercourse.</i>

2.4 PRODUCT NAME

- a) If the product owner wishes to use the formulary name, any amendments made to the product formulation such as the addition of active ingredients, removal of active ingredients or change in strength of active ingredients is not permitted.
- b) A brand name in front of the formulary name shall be requested to be added, in order to differentiate and identify their product from products with the same formulary name.
- c) Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product is prohibited.
- d) For products in which the product name is the name of active ingredient or the product name is a common name, e.g. *Kapsul Kacip Fatimah*; *Misal Kucing Tea*; *Ortosiphon Capsule*; *Herbal Rub*; *Natural Herb Capsule*, a brand name shall be added to the product name, in order to differentiate and identify this specific product.
- e) Product names which are not permitted to be registered are as specified in **Table 7** below:

No.	Non-Permissible Product Names	Example
1.	Prohibited use of disease names as stated in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983)	Example : Diabetes, Asthma, Cancer
2.	Prohibited use of a single active ingredient as a product name in products containing more than one active ingredient unless product name contains words such as 'Plus, Compound, Complex, Herbanika	Example : Tongkat Ali Capsule ---- But product contains tongkat ali, ginseng, ect.
3.	Prohibited use of superlative - Names which indicates superiority inefficacy	Example : Power/ Kuasa, Superior, Pure, Mustajab, Safe, Healthy/ Sihat, Penawar/ Shifa, VIP, Good, Heal/ Sembuh, Premium, Mustajab, Men/ Women/ Children Complete, Men/ Women/ Children Enriched, Paradise/ Syurga, Menawan

No.	Non-Permissible Product Names	Example
4.	<p>Prohibited use of spelling of words which may cause confusion Words which involve names of/part thereof:</p> <ul style="list-style-type: none"> i) 20 disease names prohibited in the Medicines (Advertisement and Sale) Act 1956 (Revised 1983) ii) Diseases without scientific evidence of efficacy/ prescription medication to treat diseases/ parameters that indicate certain diseases (e.g. insulin, glucose) iii) Prohibited indication (e.g. to detoxify body) 	<p>Example :</p> <ul style="list-style-type: none"> a) Go Out = GOUT b) UTix = Urinary Tract Infection c) Diabecine = Diabetes d) Metformon = Metformin e) Insuprem = Insulin f) Glucosey = Glucose g) DetoxB = Detox body
5.	<p>Prohibited use of names which may cause ambiguity Ambiguous product name</p>	<p>Example: B For Energy?</p>
6.	<p>Prohibited use of names which may be offensive or indecent</p>	<p>Example: SENXBIG=SEnXBIG(label) Sexy, Enjoy, Paradise, Heavenly, Blue boy, Casanova, Desire(<i>Dezire</i>), <i>Sensual</i> (<i>Xenxual</i>), <i>Asmara</i>, <i>Syok</i></p>
7.	<p>Prohibited use of product names which are incoherent with the approved indication Name containing a product claim whereas product is indicated for more than the approved indication</p>	<p>Example: Cough Syrup X= Approved indication for cough, dizziness, flu and itch</p>
8.	<p>Prohibited use of product names which has elements of ludicrous belief Statements referring to ancient believe/ negative spirits/ supernatural power</p>	<p>Example: Words such as miracle, magic, magical, miraculous, saintly, heavenly</p>

No.	Non-Permissible Product Names	Example
9.	Prohibited use of product names similar to the existing approved product names Product names similar to the spelling and pronunciation of words of the existing product names	Example: Tenormin vs Tenormine vs Tenormy Re-Liv vs Re-Lif
10.	Prohibited use of product names which may cause ambiguity in the nature of product (drug/ food/ beverage) Product names similar to a food/ beverage product	Example: Juice, Health drink, Beverage, Kooky
11.	Prohibited use of product names which represents professional advice or opinion or referring to the profession	Example: Dr Sunny, Dr Noortier Rooibose Tea, Professor, Herbalist, Doctor
12.	Prohibited use of product names which represent weight loss/ slimming properties	Example: Slim, Langsing, Trim, Trimnfit, <i>Sleen, Kurus, Susut perut</i>
13.	Prohibited use of product names referring to any religious content	Example: Maksum, Mahmudah, Arifbillah
14.	Name of internal organ	Example: Liver, Brain, Kidney, etc.
15.	Prohibited use of abbreviation as a product name	Example: TVB, PLQ
16.	Other prohibited product names	Example: Minda, IQ, Smart, Genius, Ultra Mega, Detox

Note:

The Authority reserves the right to disallow any other words or phrases for product names which in its opinion is misleading, improper or not factual.

2.5 QUALITY CONTROL

2.5.1 SAMPLE FOR TESTING

Sample for testing shall be submitted to the Drug Analysis Division, NPCB within 14 days of payment confirmation by the NPCB.

For further information, please refer **Section C: Guideline for Submission of Product Samples for Laboratory Testing** in the main DRGD.

2.5.2 APPEAL FOR SAMPLE RETESTING

Appeal for retesting must be submitted through on-line registration system within 30 days from the date the results are sent to the applicant. Samples submitted after the 30 days grace period will not be entertained. The application will then be tabled to the Authority for rejection.

2.5.3 QUALITY TESTING FOR SPECIFIC INGREDIENT

- i) For product containing *Aphanizomenon flos-aquae*, applicants would have to provide certificates of analysis showing that the microcystin-LR or total microcystins content of the raw material does not exceed 1µg/g and the finished product has been tested for microcystin-LR using an acceptable method;
- ii) For products containing Red Yeast Rice (*Monascus purpureus*), applicants shall provide certificates of analysis (for both raw material and finished product) showing the Monacolin-K content. The percentage of Monacolin-K shall not exceed 1% and the Monacolin-K consumed shall not exceed 10 mg per day.

2.5.4 LIMIT TEST FOR HEAVY METALS

Limit for heavy metals:

- i) Lead : NMT 10.0 mg/kg or 10.0 mg/litre (10.0ppm)

- ii) Arsenic : NMT 5.0 mg/kg or 5.0 mg/litre (5.0ppm)
- iii) Mercury : NMT 0.5 mg/kg or 0.5 mg/litre (0.5ppm)
- iv) Cadmium : NMT 0.3 mg/kg or 0.3 mg/litre (0.3ppm)

2.5.5 DISINTEGRATION TEST

Disintegration time for tablets, capsules and pills

- i) Uncoated tablets : NMT 30 minutes
- ii) Film-coated tablets : NMT 30 minutes
- iii) Sugar-coated tablets : NMT 60 minutes
- iv) Enteric-coated tablets : Does not disintegrate for 120 minutes in acid solution but to disintegrate within 60 minutes in buffer solution
- v) Capsules : NMT 30 minutes
- vi) Pills : NMT 120 minutes

2.5.6 TEST FOR UNIFORMITY OF WEIGHT (FOR TABLETS AND CAPSULES ONLY)

i) *Tablet*

- For tablet with average weight of 130mg or less: Not more than 2 tablets differ from the average weight by more than 10% AND no tablets differ from the average weight by more than 20%
- For tablet with average weight between 130-324mg: Not more than 2 tablets differ from the average weight by more than 7.5% AND no tablet differs from the average weights by more than 15%
- For tablets with average weight more than 324mg: Not more than 2 tablets differ from the average weight by more than 5% AND no tablet differs from the average weight by more than 10%

ii) Capsule

Individual weight of the capsule to be within the limit of 90 - 110% of the average weight.

2.5.7 TESTS FOR MICROBIAL CONTAMINATION**TABLE 8:**

Route of Administration	TAMC (CFU/g or CFU/ ml)	TYMC (CFU/g or CFU/ ml)	Test for Specified Microorganisms
Rectal Use	NMT 2×10^3	NMT 2×10^2	
Oromucosal Use Gingival Use Cutaneous Use Nasal Use Auricular Use	NMT 2×10^2	NMT 2×10^1	<ul style="list-style-type: none"> - Absence of <i>Staphylococcus aureus</i> in 1g or 1ml - Absence of <i>Pseudomonas aeruginosa</i> in 1g or 1ml
Vaginal Use	NMT 2×10^2	NMT 2×10^1	<ul style="list-style-type: none"> - Absence of <i>Staphylococcus aureus</i> in 1g or 1ml - Absence of <i>Pseudomonas aeruginosa</i> in 1g or 1ml - Absence of <i>Candida albicans</i> in 1g or 1ml
Transdermal Patches (limits for one patch including adhesive layer and backing)	NMT 2×10^2	NMT 2×10^1	<ul style="list-style-type: none"> - Absence of <i>Staphylococcus aureus</i> in 1 patch - Absence of <i>Pseudomonas aeruginosa</i> in 1 patch
Inhalation Use (Special Requirement apply to liquid preparations for nebulisation)	NMT 2×10^2	NMT 2×10^1	<ul style="list-style-type: none"> - Absence of <i>Staphylococcus aureus</i> in 1g or 1ml - Absence of <i>Pseudomonas aeruginosa</i> in 1g or 1ml - Absence of bile-tolerant gram-negative bacteria in 1g or 1ml

Route of Administration	TAMC (CFU/g or CFU/ ml)	TYMC (CFU/g or CFU/ ml)	Test for Specified Microorganisms
Special Ph. Eur. provision for oral dosage forms containing raw materials of natural (animal, vegetal or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU per gram or milliliter	NMT 2×10^4	NMT 2×10^2	<ul style="list-style-type: none"> - NMT 2×10^2 CFU of bile-tolerant gram- negative bacteria in 1g or 1ml - Absence of Salmonella in 10g or 10ml - Absence of Escherichia coli in 1g or 1ml - Absence of Staphylococcus aureus in 1g or 1ml
<p>Special Ph. Eur. provision for herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered):</p> <ul style="list-style-type: none"> - Herbal medicinal products to which boiling water is added before use - Herbal medicinal products to which boiling water is not added before use 	<p>NMT 2×10^7</p> <p>NMT 2×10^5</p>	<p>NMT 2×10^5</p> <p>NMT 2×10^4</p>	<ul style="list-style-type: none"> - NMT 2×10^2 CFU of Escherichia coli in 1g or 1ml - NMT 2×10^3 CFU of bile-tolerant gram- negative bacteria in 1g or 1ml - Absence of Escherichia coli in 1g or 1ml - Absence of Salmonella in 10g or 10ml

Notes:

TAMC : Total Aerobic Microbial Count

TYMC : Total Yeasts & Moulds Count

NMT : Not more than

[Reference: British Pharmacopoeia 2008 (Harmonised Method)]

2.6 STABILITY DATA

Stability data as shown in the following example shall be submitted for evaluation.

EXAMPLE:

STABILITY DATA

PRODUCT NAME	: TABLET ABC 500MG	BATCH NO.	:
DOSAGE FORM	:	STRENGTH/ VOLUME	:
CONTAINER/ PACKAGING	:	DATE OF REPORT	:
MANUFACTURING DATE	: dd/mm/yy	TEMPERATURE	: 30 °C ± 2 °C
EXPIRY DATE	: dd/mm/yy	RELATIVE HUMIDITY	: 75 % ± 5%

PERIOD OF STUDY:

Tests	Acceptance Criteria/ Specification	Frequency of Test, in month (<i>Kekerapan Ujian, bulan</i>)								
		0	3	6	9	12	15	18	21	24
Product description	Film-coated tablet, brownish in colour									
Disintegration test	NMT 30 minutes									

Tests	Acceptance Criteria/ Specification	Frequency of Test, in month (<i>Kekerapan Ujian, bulan</i>)								
		0	3	6	9	12	15	18	21	24
Microbial Contamination Test: - Total Aerobic Microbial Count - Total Yeasts & Moulds Count - Test for Specified Microorganisms	NMT 2×10^4 NMT 2×10^2 ➤ NMT 2×10^2 CFU of bile-tolerant gram-negative bacteria in 1g or 1ml ➤ Absence of Salmonella in 10g or 10ml ➤ Absence of Escherichia coli in 1g or 1ml ➤ Absence of Staphylococcus									

Tests	Acceptance Criteria/ Specification	Frequency of Test, in month (<i>Kekerapan Ujian, bulan</i>)								
		0	3	6	9	12	15	18	21	24
Heavy Metal Test: - Lead - Arsenic - Mercury - Cadmium	 ≤10.0 mg/kg (≤ 10ppm) ≤5.0 mg/kg (≤ 5ppm) ≤0.5 mg/kg (≤ 0.5ppm) ≤0.3 mg/kg (≤ 0.3ppm)									

Conclusion -----

Prepared by: (signature)

Name:

Designation:

Date:

Checked by: (signature)

Name:

Designation:

Date:

Approved by: (signature)

Name:

Designation:

Date:

2.7 LABELLING REQUIREMENT

- a) The following information as shown in **Table 9** shall be included in the product label. Please refer example of label for natural products approved by the Authority, as shown below.

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
1.	Product name	√	√	√	√
2.	Dosage Form	√	√	√	√
3.	Name of active ingredients, including part of plant used	√	√	√	
4.	Strength of active ingredient in weight	√	√	√	
5.	Indication	√	√		
6.	Batch number	√	√		√
7.	Manufacturing date	√	√		
8.	Expiry date	√	√		√
9.	Dosage/ Use instruction	√	√	√	
10.	Storage condition(s) - state temperature used in the stability study - state "Protect from light and moisture" (If product is not packed in moisture resistant container)	√	√	√	
11.	Registration number (MAL)	√	√		√
12.	Name and address of product registration holder (Example: Product Registration Holder: XXXXX)	√	√		

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
13.	Name and address of manufacturer (Example: Manufacturer: XXXXX)	√ At least name of town/ city and country of manufacturer	√ At least name of town/ city and country of manufacturer	√	
14.	Warning label (if applicable) a. Ginseng b. Bee pollen c. Senna (Cassia spp.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinalis – root part d. Camphor e. <i>Chelidonium majus</i> f. Alfalfa (<i>Medicago sativa</i>) g. St. John's Wort h. Black cohosh i. Propolis j. Royal jelly k. <i>Ginkgo biloba</i> / Ginkgo extract l. <i>Pelargonium sidoides</i> m. Benzyl Alcohol / Phenylmethanol (preservative) n. Red Yeast Rice o. Substance from seafood p. Other substances as listed under 2.7.2 Specific Labelling Statements/ Warning & Precautions	√	√	√	
15.	Pack size (unit/ volume)	√	√	√	
16.	Name and strength of preservative	√	√	√	

No.	Items	Immediate Label	Outer Label	Package Insert	Blister Pack
17.	Name and content of alcohol, where present	√	√		
18.	To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine (capsule shell).	√	√		
19.	Additional statement (if applicable)	√	√	√	
20.	Contraindication/ Precaution (if any)	√	√	√	
21.	Security Label (Hologram)	√	√ #		

b) All labels and package inserts must be in *Bahasa Malaysia* or English. In addition to this, translation to another language will be allowed.

c) # In case of no outer carton, the security label shall be applied to the immediate labels. The security label shall not be applied onto outer shrink wrap of a product.

d) Please ensure all requirements as specified below are stated on the labels and package inserts:

- State the weight per dosage form
- State the quantity/ content of active ingredients per dosage form
- For products in liquid form (syrup), content of active ingredients shall be stated as follows:

“Each ____ml (per dosage) product contains extract of the following ingredients”

Herb X = ____mg

Herb Y = ____mg

- Check and correct all spelling/ grammar and translations.

Example of label approved by the Authority:

This is a traditional medicine		Each Capsule (Vegetable capsule) contains :
Please consult your pharmacist/ doctor before taking this product	KAPSUL PQR	Folium XX 200mg Fructus QY 300mg
Jauhkan daripada kanak-kanak <i>Keep out of reach of children</i>	500MG	Dosage : 2 capsule taken twice a day after food
Indication: Traditionally used for women's health	MALXXXXXXXXT	
Warning: Pregnancy and breastfeeding: Insufficient reliable data	50 CAPSULE	Marketing authorization holder: Syarikat XYZ Sdn Bhd 18, Jalan Utama 47000 Sungai Buloh Selangor
Keep below 30 ° celcius Protect from light and moisture	<div>Hologram</div>	Manufactured by: Syarikat ABC Sdn Bhd 3, Jalan Universiti 46730 Petaling Jaya
Manufacturing date: Expiry date: Batch No.:		

2.7.1 STATEMENTS TO BE STATED ON PRODUCT LABEL

The following statements shall also be stated on the product label, where applicable:

- For product with an indication "For general health/ well being" **or** "*Untuk kesihatan umum*", please state:
 - "Please consult your pharmacist / doctor before taking this product **or** *Sila merujuk kepada ahli farmasi/ doktor sebelum mengambil produk ini.*"
- For product with an indication "To relieve symptoms for.... (any illness)" **or** "*untuk mengurangkan tanda-tanda/ simptom....*", please state:
 - "Please consult your pharmacist/ doctor if symptoms persist/ worsen **or** *Sila merujuk kepada ahli farmasi/ doktor jika simptom berlarutan/ bertambah teruk.*"

- “This is a traditional medicine/*Ini adalah ubat tradisional.*” **OR** “This is a homeopathy medicine/*Ini adalah ubat homeopati.*”
- Unless otherwise supported, all herbal/ traditional products label shall state the following general cautionary statement, **EXCEPT** for product with indication for men’s health or product for children use only:
 “Pregnancy and breastfeeding: Insufficient reliable data”
- For product with an indication to be taken/ used **specially for women**, please refer **2.6.3 Cautionary Statement for Products Specially Used in Women.**
- “Keep out of reach of children & *Jauhi dari kanak-kanak*” (in both *Bahasa Malaysia* and English).
- “Protect from light and moisture.”
- Please state the storage condition according to the temperature stated in stability data.
- For products containing ingredients as specified below, please add the required statements:
 - i) **Animal part(s):**
 “This product contains animal part(s).”
 - ii) **Animal origin(s):**
 “This product contains substance(s) from animal origin.”
 - iii) **Porcine:**
 “This product contains animal part(s) (porcine/ pig).”
 - iv) **Alcohol:**
 - “This product contains alcohol.”
 - Please declare the percentage of alcohol contained in the product.
- For the following dosage forms, please add this statement:
 - i) **Topical preparations:** “For external use only.”
 - ii) **Liquids and suspensions:** “Shake well before use”

2.7.2 SPECIFIC LABELLING STATEMENTS/ WARNING & PRECAUTIONS

For products containing the following active ingredients, specific cautionary statement(s) as specified shall be included:

- For product containing **Alfalfa (Medicago sativa)**, please state:

This product contains Alfalfa (Medicago sativa).

Individuals with a predisposition to systemic lupus erythematosus shall consult their physician before consuming this product.

- For product containing '**Anti-diarrhoea**', please state:

"Contraindicated in children below 1 year old."

- For product containing **Aspartame**, please state:

WARNING:

"Unsuitable for phenylketonurics"

- For products containing **BEE POLLEN**, please state:

- This product contains Bee Pollen and may cause severe allergic reactions, including fatal anaphylactic reactions in susceptible individuals.
- Asthma and allergy sufferers may be at greater risks.

- For product containing **Benzyl Alcohol/ Phenylmethanol (as preservative)**, please state:

As this preparation contains benzyl alcohol, its use shall be avoided in children under 2 years of age. Not to be used in neonates.

- For product containing **Black Cohosh (*Cimicifuga racemosa*)**, please state:

Warning:

- **Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine and consult your doctor immediately.**
- **Patients using herbal medicinal products shall tell their doctor about it.**

- For products containing **Camphor**:

- i) The following warning shall be stated on the label:

WARNING:

**CAN CAUSE CONVULSION
CONTRAINDICATED IN INFANTS BELOW 2 YEARS OF AGE.
CAUTION MUST BE EXERCISED WHEN OLDER CHILDREN ARE
TREATED.
AVOID DIRECT APPLICATION INTO NOSTRILS**

PRECAUTION:

It is dangerous to place any camphor – containing product into the nostril of children. A small amount applied this way may cause immediate collapse.

- Avoid contact with the eyes.
- Do not apply to wounds or damaged skin.

- ii) The following warning and precaution shall be stated on product leaflet:

WARNING: “This product is contraindicated in infants under 2 years of age. Caution must be exercised when older children are treated”

PRECAUTION: “It is dangerous to place any camphor containing product into the nostrils of children. A small amount applied this way may cause immediate collapse”

- For product containing **Chelidonium Majus**, please state (in *Bahasa Malaysia* & English):
 - **Warning: This Product may cause adverse reaction to the liver.**
 - **Amaran: Produk ini mungkin boleh menyebabkan kesan sampingan pada hepar (hati).**

- For products containing **GAMAT/ STICHOPUS spp.** for **ORAL USE ONLY**, please state:

“Please consult your pharmacist, doctor, or other healthcare providers about any other supplements/ medications you are taking and other health care problems. There may be a potential for interactions or side effects.”

- For product containing **Ginkgo biloba/ Ginkgo extract**, please state:

“As the use of Ginkgo may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/ dental procedure.”

(Memandangkan Ginkgo boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau sedang akan menggunakan ubat lain dan sebelum prosedur pembedahan/ dental dijalankan.)

- For products containing **GINSENG** (including all PANAX genus), please state:
 - **“Contraindicated in pregnant women.”**
 - **“Safe use in lactating women and children has not been established.”**
 - **“Do not exceed the stated dose.”**
 - **“Safety on long term use has not been established.”**

- For product containing **Momordica Charantia**, please state:
 - **“Shall not be used in pregnant and breast-feeding women.”**
 - **“Be sure to tell your pharmacist, doctor, or other healthcare providers about any other supplements you are taking. There may be a potential for interactions or side effects.”**

- For product containing **Pelargonium sidoides**, please state:

In very rare cases, pelargonium sidoides may cause hypersensitivity reactions

- For product containing **Propolis (topical preparation)**, please state:
“Propolis may cause allergic skin reaction.”
- For product containing **Propolis (for oral use)**, please state:
 - **“This product contains propolis and may cause severe allergic reactions including fatal anaphylactic reaction in susceptible individuals.”**
 - **“Asthma and allergy sufferers may be at a greater risk.”**
- For products containing **Psyllium/ Plantago (Seed/ Husk)**, please state:
 - **“If the constipation does not resolve within 3 days or if abdominal pain occurs or in case of any irregularity of faeces, the use of psyllium should be discontinued and medical advice must be sought.”**
 - **“Please consume a large amount of fluid/ water when taking this product.”**

- For product containing **Royal Jelly (for oral use)**, please state:
 - **“This product contains royal jelly and may cause severe allergic reactions including fatal anaphylactic reaction in susceptible individuals.”**
 - **“Asthma and allergy sufferers may be at a greater risk.”**
- For product containing **naturally occurring SALICYLIC ACID** (e.g. Willow *Salix* spp.), please state:
 - **“People allergic to aspirin/ other NSAID should avoid this product.”**
- For products containing **Senna (Cassia spp.) – fruit/ pod/ semen and leaf** and **Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinale – root part**, please state:
 - **“Do not use when abdominal pain, nausea or vomiting is present.”**
 - **“Frequent or prolonged use of this preparation may result in dependence towards the product and ‘imbalanced electrolytes’.”**
 - **“Please consult a healthcare practitioner for use beyond 7 days.”**
- For product containing **St. John’s Wort**, please state:

<p>The product may interact with other medicines. Please consult a doctor/ pharmacist before using it.</p>

- For product containing **substance from seafood**, please state:

“Derived from seafood.”
- For product with indication **“To regulate menstruation/ To improve menstrual flow”**, please state:

“Contraindicated in pregnant women.”

- For product with indication **‘To reduce body weight’**, please state these statements, (unless proven otherwise):
 - **“Balanced diet and regular exercise are essential.”**
 - **“Safety on long term use has not been established.”**
- For product containing **Red Yeast Rice**, please state:

“This product contains naturally occurring lovastatin. Please consult your doctor/ pharmacist before using this product.”

“Do not take this product if you are already on statin products (lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, rosuvastatin,etc).”

“If you experience any allergic reactions or side effects such as lethargy, body and muscle aches, please stop using this product.”

“Concurrent use of fibrates may cause severe myositis and myoglobinuria.”

2.7.3 CAUTIONARY STATEMENT FOR PRODUCTS SPECIALLY USED IN WOMEN

Special precaution shall be given to ingredients taken during pregnancy. The Authority urges pregnant women to consult their medical/ traditional health care provider prior to taking any herbal or traditional products.

Unless otherwise supported, all herbal/ traditional products label shall state the following general cautionary statement:

“Pregnancy and breastfeeding: Insufficient reliable data”

However, for products containing any ingredients as listed in the following lists, i.e. List of Prohibited Ingredients in Pregnancy and List of Restricted Ingredients in Pregnancy, the following cautionary statement shall be stated in the product label:

- i) Prohibited Ingredients in Pregnancy:
“Contraindicated in pregnant women.”
- ii) Restricted Ingredients in Pregnancy:
“To be used with caution in pregnancy.”

The list of herbs contraindicated in pregnancy is rarely in agreement as most herbal products are used in combination. The following list has been compiled based on well documented information as an aid to the industry to comply with the labelling requirement for products used during pregnancy.

Table 10: List of Prohibited Ingredients in Pregnancy

	Latin Compendium Name	Common/ Chinese Name	Remarks
A	Acorus Calamus	Calamus	
	Achillea Millefolium	Yarrow	
	Angelica Archangelica	Angelica	
	Angelica sinensis	Dong Quai	When taken orally
	Artemisia Vulgaris	Mugwort	
	Arctostaphylos Uva Ursi	Uva Ursi	
	Artemisia Absinthium	Wormwood	
	Astragalus gummifer	Tragacanth	
B	Bryonia Alba	White Bryony	
	Bupleurum chinense, Bupleurum falcatum	Bupleurum	
C	Calendula Officinalis	Calendula	
	Capsella Bursa-Pastoris	Shepherd's Purse	
	Cassia Marilandica	Senna	
	Caulophyllum Thalictroides	Blue Cohosh	When taken orally
	Chamaemelum nobile (Anthemis nobilis)	Roman Chamomile	When taken orally
	Chenopodium Ambrosioides	Epazote	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Cichorium intybus	Chicory	
	Cimicifuga Racemosa	Black Cohosh	When taken orally
	Cnicus Benedictus	Blessed Thistle	
	Conium maculatum	Hemlock	
	Convallaria Majalis	Lily of the Valley	
	Cortex Cinnamomi	Rou Gui	
	Cortex Moutan	Mu Dan Pi	
	Crocus Sativus	Saffron	
E	Equisetum arvense L.	Horsetail	
F	Flos Carthami	Hong Hua	
	Flos Genkwa	Yuan Hua	
	Folium Sennae	Fan Xie Ye	
	Fructus Aurantii	Zhi Ke	
	Fructus Aurantii Immaturus	Zhi Shi	
G	Gentiana lutea	Gentian	
	Ginkgo Biloba	Ginkgo	
H	Helleborus spp.	Hellebore	
I	Iris Versicolor	Blue Flag	
	Ipecac Ipecachuana	Ipecac	
J	Juglans Canadensis	Butternut	
	Juglans nigra	Black Walnut	
	Juniper (<i>Juniperus communis</i>)	Juniper Berries	
L	Leonurus Cardiaca	Motherwort	
M	Marrubium Vulgare	Horehound	
	Mentha Pulegium	Pennyroyal	When used orally or topically
	Monarda didyma	Bee Balm	
	Myiobris / Radix Sacchari Arundinacei	Ban Mao	

	Latin Compendium Name	Common/ Chinese Name	Remarks
N	Natrii Sulfas	Mang Xiao	
	Nepeta cataria	Catnip	
O	Oenothera biennis L.	Evening Primrose	
P	Panax Ginseng, Panax Quinquefolius	Ginseng	
	Passiflora incarnata L.	Passion Flower	When taken orally
	Petroselinum Crispum	Parsley	
	Podophyllum Peltatum	American Mandrake	
	Polygala Senega	Senega Snakeroot	
R	Radix Euphorbiae Pekinensis	Jing Da Ji	
	Radix et Rhizoma Rhei	Da Huang	
	Radix Kansui/ Radix Euphorbiae Kansui	Gan Sui	
	Radix Phytolaccae	Shang Lu	
	Rhizoma Sparganii	San Leng	
	Resina Toxicodendri/ Resina Rhois Praeparata	Gan Qi	
	Rhizome et Radix Veratri	Li Lu	
	Radix Achyranthis Bidentatae	Niu Xi	
	Rhizome Chuanxiong	Chuan Xiong	
	Rhizome Curcumae Longae	Jiang Huang	
	Rhamnus Purshiana	Cascara Sagrada	
	Rhamnus Frangula	Buckthorn	
	Rheum Palmatum	Rhubarb Root	
	Ruta Graveolens	Rue	
	Rheum Australe	Turkey Rhubarb	
S	Sanguinaria Canadensis	Bloodroot	

	Latin Compendium Name	Common/ Chinese Name	Remarks
	Semen Pharbitidis	Qian Niu Zi	
	Semen Strychni	Ma Qian Zi	
	Semen Persicae	Tao Ren	
	Serenoa repens	Saw Palmetto	When taken orally
T	Tabebuia impetiginosa	Pay D' Arco	When taken orally
	Tanacetum parthenium	Feverfew	
	Tanacetum Vulgare	Tansy	
	Thuja Occidentalis	Arbor Vitae	
	Turnera Diffusa	Damiana	
	Trigonella foenum-graecum	Fenugreek	
	Trillium Erectum	Bethroot	
	Tussilago Farfara	Coltsfoot	
V	Venenum Bufonis	Chan Su	
	Viscum Album	European Mistletoe	
X	Xanthoxylum Americanum	Prickley Ash	

Table 11: Restricted in Pregnancy

No.	Latin Compendium Name	Common/ Chinese Name	Remarks
1.	Zingiber Officinalis	Ginger	> 1g dry weight/day

2.7.4 PROHIBITED VISUAL/ GRAPHICS/ STATEMENT ON PACKAGING MATERIAL (LABEL, BOX, PACKAGE INSERT OR PATIENT INFORMATION LEAFLET)

General requirement:

The graphics printed on outer and inner label has to be standardized to avoid confusion to the customers.

Table 12:

No.	Subject Matter	Example(s)	Notes
1.	Marketing strategy	Example: “Money back guarantee” “Buy 1 free 1” “ Backed by RM5 million product Liability Insurance”	Such statements are prohibited on labels, as per Medicines (Advertisement and Sale) Act 1956 requirements
2.	Usage guide which promotes use of other product(s)	Example: “After consumption of this product (Product A), for better results, it is recommended to take Product B”	Not allowed
3.	Consumer testimonial		Prohibited on product label

No.	Subject Matter	Example(s)	Notes
4.	Clinical Trial results or any information on clinical trial done on product	Example: “Clinically Tested” “Randomized Double Blind Placebo Control Clinical Study”	Such statements are prohibited on labels, as per Medicines (Advertisement and Sale) Act 1956 requirement
5.	Photograph of product pioneer		Not allowed
6.	Reference to Hadith/ Al-Quran/ Bible/ Religious books		Prohibited on product label
7.	Opinion of prominent figure(s) on product or its active ingredient/ content	Example: Opinion of product/ formulation inventor	Prohibited on product label
8.	Label design (graphic and color) similar to labels from another company		Prohibited on product label
9.	Statement on herbal origin	Example: Source from the Mountains of Alps	Allowed if proven true

No.	Subject Matter	Example(s)	Notes
10.	Introduction/ description of founder/ manufacturer i.e. elaboration on the identity of the founder or manufacturer	Example: “Manufacturer ABC is a GMP certified manufacturer and has manufactured many products.” “Founder Dr. ABC is a world renowned surgeon.”	Prohibited on product label
11.	Logo with certification	Example: SIRIM/ ISO / GMP /HACCP	Prohibited on product label because certification renewal is on a yearly basis
12.	Name/ Statement / Logo/ registered trademark which does not satisfy the specifications of the Traditional Unit	Example: “Dr.ABC’s Formula” “Nothing like it”	Prohibited on product label
13.	Patency claim/ Patency number/ Special technique used/ superiority in ingredients (Example: capsule coat)	Example: Patented technique	Allowed if proven true
14.	Nutritional claims with analysis certificate attached	Example: Calorie, Fat, Protein and others	Prohibited on product label This is not a food supplement.

No.	Subject Matter	Example(s)	Notes
15.	Graphics or picture of internal organs	Example: Kidney, Heart, Nerves.	Prohibited on product label
16.	Photograph of celebrities	Example: Artiste, Sports person(s), Politician	Prohibited on product label
17.	Sex symbol (male or female)	(♀ and / or ♂)	Prohibited on product label
18.	Indecent photographs/ pornography		Prohibited on product label
19.	Graphics which are incoherent with the indication	Example: <ul style="list-style-type: none"> - Noted indication is for constipation, but graphics on label shows a slim-looking lady which denotes indication for weight loss - Indication for urination but label graphics contains picture of a water hose. 	Prohibited on product label
20.	Highlighting unnecessary body parts	Example: Indication is for general health	Prohibited on product label

No.	Subject Matter	Example(s)	Notes
		but graphics on label highlights male and female sexual organ parts	
21.	Graphics of plants or animal which may cause confusion	Example: Radix Ginseng which is improvised as a male sexual organ	Prohibited on product label
22.	Statement on sugars in traditional products	Example: - This product contains no sugar -This product contains no added sugar	Allowable on product label provided the product contains no fructose, glucose, sucrose or other kind of sugars with a potential to affect diabetics are not included in the formulation
23.	Other statements	Example: - This product is blended with premium quality - Certified chemical residue free	Prohibited on product label

Notes:

The Authority reserves the right to disallow any other words, phrases or graphics for product label which in its opinion is misleading, improper or not factual.

3. PRODUCT SPECIFIC REQUIREMENTS

3.1 FOOT PATCHES

A foot patch which contains herbs with a health claim needs to be registered with the Authority.

Summary of registration for foot patches is described below:

a) Product Indication

- Traditionally used for
 - a) General health;
 - b) Promoting blood circulation;
 - c) Relieve fatigue.
- If there are other indications other than those mentioned above, applicant is required to submit clinical study data to support the proposed indication.

b) Active ingredient/ Excipient

- May only contain active ingredient which are classified under the category of Natural Products (Traditional).
- Pharmaceutical ingredients which have dual-function as an active ingredient and excipient, e.g. Vitamin C can be used as excipient.
- However the maximum allowable amount for the excipient in the traditional product has to follow the pharmacopoeia limits established. If for example in this case the amount of Vitamin C is more than 0.1%, the product shall be classified as an OTC product. The product will then have to fulfill the requirement for the registration of an OTC product.

c) Certificate of Analysis for Finished Product

- It is required with at least one batch data for registration.

d) Certificate For Free Sale

- CFS from the regulatory authority of the country of origin of the product depending on the product classification of that product in that country

e) Good Manufacturing Practice

- GMP from the governmental issuing body declaring manufacturer adherence to GMP/ ISO or other standards depending on the classification of the product in the country of origin.

(Reference: [Circular Bil.\(3\)d/m.BP/PP/01/03Jld.1](#))

1.2 HERBAL TEA

- a) Raw or crude herbs that contain more than 20% of active ingredients and has a therapeutic or pharmacological effect will be controlled under NPCB;
- b) Raw or crude herbs that are less than 20% of total active ingredient and are normally consumed as food will be controlled under the Food Service Division, Ministry of Health;
- c) Active ingredients in extract forms will have to be registered irrespective of the amount present in the finished product.

(Reference: [Circular \(92\)d/m.BP/PP/01/03 Jilid 2](#))

3.3 HOMEOPATHIC PRODUCTS

The following guidance notes are published as [First Edition in October 2010](#) and the latest revision is on October 2012.

This guidance notes serve as an additional reference on the requirements for the registration of homeopathic products. Other aspects of registration requirements are covered in the Drug Registration Guidance Document. Applicants for product registration are also requested to refer to the latest edition on the Guidelines of Good Manufacturing Practices (GMP) for Traditional Medicines.

2nd Revision

Acknowledgements

The National Pharmaceutical Control Bureau acknowledges its indebtedness to the Malaysia Homeopathic Medical Council and the Traditional & Complementary Medicine Division, Ministry of Health who provided comments and advice during the preparation of these guidelines.

Outline:

1. Introduction
2. Exemptions
3. Preparations not considered by the Authority for registration
4. Ingredients
5. Quality
6. Good Manufacturing Practice
7. Labelling
8. Indications for use

Attachments:

- Attachment 1: List of exempted Single Homeopathic Potentised Dilutions
- Attachment 2: Negative List
- Attachment 3: List of acceptable references
- Attachment 4: List of endangered animal species/ protected wildlife

1. INTRODUCTION

Regulation 7(1)(a) of the Control of Drugs and Cosmetics Regulations (CDCR) 1984 requires all products to be registered with the Authority prior to being manufactured, sold, supplied, imported or possessed for sale, unless the product is exempted under the specific provisions of the regulations.

Under Regulation 2, CDCR 1984, “**Homeopathic medicine**” means any pharmaceutical dosage form used in the homeopathic therapeutic in which diseases are treated by the use of minute amounts of such substances which are capable of producing in healthy persons symptoms similar to those of the disease being treated. This would include preparations that are to be chewed, sucked, swallowed whole and applied topically.

Applicants are reminded that it is their responsibility to ensure that their products comply with these regulations and also other related legislations namely:

- (i) Sale of Drugs Act 1952
- (ii) Dangerous Drugs Act 1952
- (iii) Poisons Act 1952
- (iv) Medicines (Advertisement & Sale) Act 1956
- (v) Wildlife Protection Act 1972

2. EXEMPTION

All homeopathic products are registrable under the *Control of Drugs and Cosmetics Regulations 1984*. Exemption to this are:

- i) single homeopathic potentised dilution;
- ii) extemporaneous preparation for an individual patient by a registered/ licensed homeopathic practitioner;
- iii) All Mother Tinctures;
- iv) Unmedicated sugar globules and tablets.

3. PREPARATION NOT CONSIDERED BY THE AUTHORITY FOR REGISTRATION

The Authority will only register homeopathic products used for oral administration, nasal or mouth sprays and external application only. The following dosage forms will not be considered for registration.

- Sterile preparations such as eye-drops and injectables;

- Suppositories and vaginal tablets;
- Transdermal patch;
- Sublingual preparations;
- Preparation in combination with non-homeopathic active ingredient, such as vitamins, minerals and herbs.
- Preparations containing substance listed in the Poison List (except **Attachment 1**).

4. INGREDIENTS

Homeopathic products are prepared from natural or synthetic sources that are referenced in pharmacopoeia monographs or other recognized documents. Not considering imponderable, the source materials for homeopathic medicines may consist of the following:

- Plant material such as: roots, stems, leaves, flowers, bark, pollen, lichen, moss, ferns and algae;
- Microorganisms such as: fungi, and plant parasites;
- Animal materials such as: whole animals, animal organs, tissues, secretions;
- Minerals and chemicals.

For each medicinal ingredient, a copy of the monograph from the pharmacopoeia to which the applicant attests must be provided. Also for homeopathic medicines with a specific claim, it must be supported by the same level of evidence as for traditional products.

Products containing a combination of homeopathic and non-homeopathic medicinal ingredient will not be evaluated as a homeopathic product.

4.1 POSITIVE LIST

Homeopathic medicinal ingredients are allowed as multi ingredient in homeopathic products and the active ingredient must be documented in a monograph as a homeopathic medicinal ingredient as stated in the current edition of Homeopathic Pharmacopoeias recognized by the Authority listed in **Attachment 3**.

Homeopathic products are allowed to be registered when the homeopathic medicinal ingredients used in their products are more than 2C or 4X.

4.2 NEGATIVE LIST

Homeopathic products containing single or multiple ingredients in **Attachment 2** and **Attachment 4** will not be registered by the Authority.

4.3 LIMIT OF HOMEOPATHIC INGREDIENTS IN MULTI INGREDIENT HOMEOPATHIC PRODUCTS

Homeopathic Products are allowed to contain a maximum of 12 potentised single homeopathic dilutions.

5. QUALITY

A certificate of analysis (CoA) for raw material potentised dilution and finished product must be provided as proof on the dilution used.

6. GOOD MANUFACTURING PRACTICE

The requirements for Good Manufacturing Practice of the premises as outlined in the Guidelines on Good Manufacturing Practice (GMP) for Traditional Medicines apply to all homeopathic products.

7. LABELLING

The labelling of homeopathic products is the same as for traditional products in DRGD with the following additional requirements:

On the label of this homeopathic product:

- a) The word 'homeopathic product', 'homeopathic medicine', 'homeopathic preparation', 'homeopathic remedy' (either one) - must appear on the innermost label of the container.
- b) The scientific name or common name of the active ingredient.
- c) Potency and type of scale use.
- d) Declare the percentage of alcohol contained in the product.

8. INDICATIONS FOR USE

Indications allowed for homeopathic product is the same as those allowed for traditional products in the DRGD.

Recommended use or indications for specific claims must be supported by evidence for the multi ingredient homeopathic products.

No indication will be allowed for single homeopathic potentised dilution in the form of raw material and finished homeopathic product. No indications are also allowed for mother tinctures.

ATTACHMENTS

Attachment 1:

List of “Single Homeopathic Potentised Dilution (2C or 4X or 1:10000)” exempted from the Poisons List.

No.	Ingredient
1.	Aconite
2.	Amyl nitrite
3.	Antimony
4.	Apomorphine
5.	Arsenic
6.	Barium
7.	Belladonna
8.	Bismuth
9.	Boric Acid
10.	Caffeine
11.	Cantharidin
12.	Colchicine
13.	Coniine
14.	Creosote
15.	Curare
16.	Digitalis

No.	Ingredient
17.	Ephedra
18.	Ergot
19.	Gelsemium
20.	Hydrogen Cyanide
21.	Hyoscine
22.	Iodine
23.	Jaborandi
24.	Lead Acetate
25.	Lobelia Inflata
26.	Mercury
27.	Morphine
28.	Nicotine
29.	Nux Vomica
30.	Phosphorus
31.	Physostigmine
32.	Picric Acid
33.	Piper Methysticum (Kava-kava)
34.	Quebracho
35.	Quinine
36.	Radium
37.	Rauwolfia
38.	Sabadilla
39.	Santonin
40.	Sparteine
41.	Stavesacre
42.	Strophanthus
43.	Thallium
44.	Veratrum
45.	Vinca
46.	Yohimba

Attachment 2:**Negative List**

NO.	SUBSTANCES
1.	Mother tincture of Narcotics
	Homeopathic Products
	Cannabis
	Cocainum
	Cocainum muriaticum
	Coca leaves
	Narceinum
	Opium
2.	Mother tincture of Radiopharmaceuticals
	Uranium
	X-ray
3.	Mother tincture of Animal materials: Nosodes, toxins and blood products
4.	Mother tincture of human or human organ
5.	Mother tincture of Bacteria
6.	Mother tincture of Viruses

Attachment 3:**Homeopathic Pharmacopoeia from the Following Countries Will Be Accepted as References**

NO.	COUNTRIES
1.	Germany (GHP)
2.	Britain
3.	France (Phf)
4.	USA (HPUS)
5.	Pakistan

NO.	COUNTRIES
6.	India (HPI)
7.	European Pharmacopoeia

Attachment 4:**List of Endangered Animal Species/ Protected Wildlife**

As listed in the Wildlife Protection Act.

Notes:

These lists are not exhaustive and will be amended from time to time as and when the need arises

REFERENCES**a) List of Ingredients Prohibited and Restricted in Pregnancy**

1. Benchmarks for training in traditional Chinese medicine (WHO)
2. American Pregnancy Association
3. Natural Standards
4. Health Canada
5. TCM Discovery (Contraindication of Chinese Medicinal Herbs)
6. Motherlove Herbal Company (Herbs to avoid while Pregnant)
7. Green Earth Herbs (Herbs Contraindicated in Pregnancy)
8. Home. Caregroup.Org (Herbs during Pregnancy and Lactation)

b) Homeopathic Products:

1. Safety Issues in the Preparation of Homeopathic Medicines, World Health Organization, 2009.

APPENDIX 6:

GUIDELINE ON REGULATORY CONTROL OF ACTIVE PHARMACEUTICAL INGREDIENTS (API)

(Version 2.1)

Outline:

1. Introduction

2. Definition

2.1 Definition of Active Pharmaceutical Ingredient (API)

2.2 Classification of Active Pharmaceutical Ingredient (API)

3. Scope

4. Procedure for Submission

4.1 How to Submit

4.2 Required Information

4.3 Other Considerations

4.4 Processing Fee

5. Drug Master File (DMF)

6. Certificates of Suitability (CEP)

7. Full Details of API Information in the Product Dossier Application

8. Stability Data of API

9. Site Inspection

10. Maintenance of Approval Status

1. INTRODUCTION

- 1.1. A significant part of the quality of a finished pharmaceutical product is dependent on the quality of the Active Pharmaceutical ingredients (APIs) used for its formulation. Thus, a proper system of qualification of suppliers is necessary to ensure a constant sourcing of APIs of appropriate quality and to safeguard the public health interests. This will be done through standardized quality assessment and inspection procedures.
- 1.2. The National Pharmaceutical Control Bureau (NPCB) under the purview of the Ministry of Health Malaysia will introduce mandatory control of APIs as part of the requirements in the product registration application. This will be implemented prospectively according to a phased timeline established by the NPCB.
- 1.3. The implementation will begin with voluntary submission for New Chemical Entities in April 2011 and followed by;
 - Phase 1 - New Chemical Entity (mandatory in Jan 2012)
 - Phase 2 - Scheduled Poison, (to be determined)
 - Phase 3 - Non-scheduled Poison (to be determined)
- 1.4. The procedure for control of APIs established by the NPCB is based on the following principles:
 - A general understanding of the production and quality control activities of the manufacturer;
 - Assessment of API data and information, including changes and variations, submitted by the product registration holder (PRH)/ API manufacturer. These data should include the manufacturing process, material specifications and test data and results;
 - Assessment of the manufacturing site(s) for consistency in production and quality control of raw materials, with specific emphasis on key raw materials and APIs during and after purification through compliance with Good Manufacturing Practice (GMP);
 - Random sampling and testing of APIs (post-marketing surveillance);
 - Handling of complaints and recalls; and
 - Monitoring of complaints from other agencies and countries.
- 1.5. This guideline is intended to provide guidance regarding the requirements to be included for APIs in the quality part of the product dossier.

2. DEFINITION

2.1 DEFINITION OF ACTIVE PHARMACEUTICAL INGREDIENT (API)

- Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used so, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body ([WHO Technical Report Series No.970,2012](#)).

2.2 CLASSIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENT (API)

API classification can be divided into:

- Inorganic substances;
- Organic substances (isolated from materials of animal or human origin); and
- Organic substances (synthetic or semi-synthetic or isolated from herbal sources or micro-organisms).

3. SCOPE

- 3.1. This Guideline encompasses the APIs of new products for registration. This is applicable to all pharmaceutical products (excluding traditional products, veterinary products, and health supplement products) both locally manufactured and imported.
- 3.2. Biological active substances and immunological active substances are excluded from the scope of this Guideline.
- 3.3. APIs used in products for export only (FEO) are exempted from the requirement for submission of the Drug Master File (DMF) and Certification of Suitability (CEP) in the product application.
- 3.4. The DMF and CEP are only applicable for final APIs and not API intermediates.
- 3.5. Separate registration of the APIs is not a requirement for the purpose of product registration. However, the required technical documentation

pertaining to each API should be submitted with the new online product registration application.

- 3.6. Assessment of an API will be performed once submission of an application for registration of a product using the said API is made by a Product Registration Holder.

4. PROCEDURE FOR SUBMISSION

4.1 HOW TO SUBMIT

- 4.1.1 The PRH of the product registration shall submit Part 2.S ACTD as part of product application. Where any information required as per ACTD is not available the DMF will be required.
- 4.1.2 The DMF may be submitted via an electronic copy (CD) or a hardcopy (optional) directly to the NPCB to maintain confidentiality of the contents.
- 4.1.3 The NPCB may accept a CEP issued by European Directorate for the Quality of Medicine (EDQM) in lieu of the DMF of an API.

4.2 REQUIRED INFORMATION

The API information can be submitted to National Pharmaceutical Control Bureau (NPCB) in one of the following three options:

- Option 1: Drug Master File (DMF) procedure; or
- Option 2: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 3: Full details of “Part II S ACTD” in the Product Dossier

The applicant should clearly indicate at the beginning of the API section (in the Product Dossier) how the information on the API for each API manufacturer is being submitted. The API information submitted by the applicant/ FPP manufacturer should include the following for each of the options used.

4.2.1 Documents required:

Documents required for each option of API Information submission are summarized as in table below:

Table 1:

Summary of documents required for API Information Submission:

Option	Documents required
Option 1 (DMF)	<ul style="list-style-type: none"> • Part II S ACTD via the online system (Open Part only) • DMF (<i>See Section 5 for details</i>). • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and, • Certificates of Analysis of API from API Manufacturer and product manufacturer (2 batches).
Option 2 (CEP)	<ul style="list-style-type: none"> • Part II S ACTD via the online system (as deemed appropriate) • CEP (<i>See Section 6 for details</i>); and, • Certificates of Analysis of API from API Manufacturer and product manufacturer (2 batches).
Option 3 (Full ACTD)	<ul style="list-style-type: none"> • Full details of Part II S ACTD (<i>See Section 7 for details</i>) • Current GMP certificate or any other evidence of GMP compliance from a regulatory authority; and, • Certificates of Analysis of API from API Manufacturer and product manufacturer (2 batches).

4.2.2 In order to gain approval for an API;

- The data should be sufficient to justify the specifications and testing of the API (including validated analytical methods).
- The information should confirm the identity and stability of the API by providing appropriate structure elucidation and stability studies; and,

- The control of the API manufacturing process as well as the ability to produce an API with reproducible physical properties and impurity profiles should be demonstrated.

4.2.3 Any additional information regarding the API shall be requested by the NPCB, as deemed necessary.

4.3 Other considerations

In the spirit of harmonisation of regulatory activities and optimisation of efficient assessment, The NPCB will take into consideration the evaluation of relevant APIs by the regulatory authorities of the reference countries (Australia, Japan, France, Switzerland, United Kingdom, Canada, Sweden, and the United State of America) and, other PIC/S countries and World Health Organization (WHO).

4.4 Processing Fee

Not required as the API application is already incorporated in the application for product registration.

5. DRUG MASTER FILE (DMF)

- 5.1. The Drug Master File (DMF) is a document that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs.
- 5.2. The DMF submitted to the NPCB should contain the information as required under sections listed in Part 2.S ACTD.
- 5.3. Technical contents of a DMF are reviewed only in connection with the review of a new application for product registration
- 5.4. DMF's are generally created to allow an authorized party other than the holder of the DMF to refer the DMF without disclosing to any other party the contents of the file.

- 5.5. The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR) provide details on the information to be included in the API sections of an application dossier.
- 5.6. Where the drug substance and the drug product are manufactured by the same company, information on the production, quality control and stability of the drug substance may be submitted as part of the dossier for the drug product (ACTD) rather than in a separate DMF. However, the company is not precluded from submitting a DMF for the drug substance if it prefers to do so.
- 5.7. The DMF is divided into two parts, namely the Open (or PRH's) part and the Closed (or confidential) part.
- 5.8 The documents required for an application making a reference to a DMF are as follows:

- **From the PRH:**

- Open part of the DMF *from the PRH*, as part of the submitted product dossier (the open part contains most of the information in Part 2.S (ACTD) - i.e. sections S1, S2.1 and S3 to S7);
 - S1 General Information
 - 1.1 Nomenclature
 - 1.2 Structure
 - 1.3 General Properties
 - S2 Manufacture
 - 2.1 Manufacture(s)/Site of Manufacture
 - S3 Characterisation
 - 3.1 Elucidation of Structure and other Characteristics
 - 3.2 Impurities
 - S4 Control of API/Drug Substance
 - 4.1 Specification
 - 4.2 Analytical Procedures
 - 4.3 Validation of Analytical Procedures
 - 4.4 Batch Analysis
 - 4.5 Justification of Specification
 - S5 Reference Standards or Materials
 - S6 Container Closure System
 - S7 Stability

- **From the API Manufacturer:**

- The complete (open part and closed part) DMF from the API manufacturer. The closed part contains the confidential information in section Part 2.S.2. ACTD - i.e. section 2);

- S2 Manufacture
 - 2.1 Manufacture(s)/ Site of Manufacture
 - 2.2 Description of Manufacturing Process and Process Controls
 - 2.3 Control of Materials
 - 2.4 Controls of Critical Steps and intermediates
 - 2.5 Process Validation and/or Evaluation
 - 2.6 Manufacturing Process Development
- An original Letter of Access (see below).
 The Letter of Access authorizes the NPCB to refer to the DMF, in support of the application for a drug product. Thus, the Letter of Access must state the following:
 - The name of the drug product (product name, dosage form and product strength) to be registered;
 - The local PRH responsible for finished product registration; and,
 - A declaration that both the local PRH and the NPCB shall be notified of any change in the API specification or in the manufacturing process that will likely affect the product's quality or safety.

It is the responsibility of the applicant to ensure that the complete DMF (i.e. both the applicant's *Open part* and the API manufacturer's *closed part*) is supplied to NPCB directly by the API manufacturer and that the applicant has access to the relevant information in the DMF concerning the current manufacture of the API.

- 5.9. The API Manufacturer may submit the DMF via electronic copy (CD) or hardcopy (optional) directly to the NPCB to maintain confidentiality of the contents. The information contained in the restricted part of the DMF will be regarded as confidential and will only be evaluated in support of the applications mentioned in the Letter of Access. The confidential information will not be disclosed to any third party without a written authorization from the API Manufacturer.
- 5.10. Upon receipt of the DMF, a BPFK DMF number will be assigned to the application for product registration. For future correspondences, the PRH and the API Manufacture should make a reference to this assigned BPFK DMF number. Should there be deficiencies within the restricted part of the DMF; The NPCB will raise queries directly with the API Manufacturer. The PRH referencing a DMF is required to include a copy of the API Manufacturer's Letter of Access in the application.

- 5.11. API Manufacturer is responsible to maintain and update the DMF. The PRH should file a variation once they are notified with the changes to the DMF.
- 5.12. API Manufacturer Obligations:
- Any change or addition, including a change in authorization related to specific PRH, shall be submitted to the NPCB in duplicate and adequately cross-referenced to previous submission(s). The reference should include the date(s), volume(s), section(s), and/or page number(s) affected.
 - Should any change to a DMF is necessary, the API Manufacturer shall notify each affected PRH who has referenced the DMF of the pertinent change. Such notice should be provided well before making the change in order to permit the PRH to supplement or amend any affected application(s) as needed.
- 5.13. A DMF is not required for common inorganic salts (for example, sodium chloride, and other common electrolytes) used and regarded as API in products such as injections and dialysis solutions, and simple organic compounds available commercially in high purity (for example, natural occurring organic acids and their salts, including ascorbic acid and sodium citrate, and simple mono- and disaccharides such as glucose and sucrose). Although a DMF is not required for these active ingredients, evidence needs to be submitted by the finished PRH that the substance is obtained from a reliable source and consistently comply with the applicable pharmacopoeial specifications. Any non-pharmacopoeial specifications need to be assessed by the NPCB to determine their appropriateness and adequacy to ensure the quality of the substance.
- 5.14. Where a DMF is submitted for an API controlled according to a pharmacopoeia monograph, the DMF should include a discussion of the potential impurities most likely to arise during synthesis using the actual manufacturing process described in the DMF together with evidence that these impurities are adequately controlled by the test procedures described in the pharmacopoeial monograph. Where particular impurities found in the substance are not listed in the monograph, a justification (including toxicological data, if appropriate) should be provided. Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C guidelines.

6. CERTIFICATES OF SUITABILITY (CEP)

- 6.1. CEP stands for certification of suitability of European Pharmacopoeia monographs/ Certificate of Pharmacopoeia.
- 6.2. The CEP is a document that is used to demonstrate that the purity of a given substance produced by a given manufacturer is suitably controlled by the relevant monograph(s) of the European Pharmacopoeia. By demonstrating grant a CEP for given API, the suppliers of the API can prove such suitability to their pharmaceutical industry clients and the NPCB.
- 6.3. The PRH should include a copy of the most current CEP in the dossier, together with the following:
- A written assurance that no significant changes in the manufacturing methods or processing have taken place following the granting of the certificate or its last revision and
 - A declaration from the API manufacturer that the local PRH and the NPCB shall be notified should there be any future change in the API specifications in the manufacturing process that is likely to affect the product's quality or safety.

Note: *All such written statements must state the name of the drug product (product name, dosage form and product strength) to be registered and the local PRH responsible for finished product registration.*

- 6.4 If reference is made to a CEP, the PRH should submit a copy of the valid CEP, including all annexes, in lieu of a DMF.

Along with the CEP, the applicant should supply the following information in the product dossier.

- **3.2.S.1.3 General properties** - discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section.
- **3.2.S.3.1 Elucidation of structure and other characteristics** - studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.

- **3.2.S.4.1 Specification** - the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
- **3.2.S.4.2/ S.4.3 Analytical procedures and validation** – for any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.
- **3.2.S.4.4 Batch analysis** - results from two batches of at least pilot scale, demonstrating compliance with Ph. Eur. monograph and including any additional tests/ limits listed on the CEP (e.g. residual solvents, additional impurity tests) or the product manufacturer's API specifications.
 * *In cases where the drug product manufacturer tests the CEP certified API according to specification other than Ph.Eur. (i.e. USP, JP, In-House etc.) data covering S 4.1 to S4.5 should be submitted by the PRH.*
- **3.2.S.5 Reference standards or materials** – information on the FPP Manufacturer's reference standards.
- **3.2.S.6 Container closure system** - specifications including descriptions and identification of primary packaging components.
Exception: where the CEP specifies a container closure system and the applicant declares to use the same container closure system.
- **3.2.S.7 Stability** - exception: where the CEP specifies a re-test period that is the same as or of longer duration, and storage conditions which are the same or higher temperature and humidity as proposed by the applicant.

In the case of sterile APIs, data on the sterilization process of the API, including validation data, should be included in the PD.

- 6.5 The NPCB reserves the right to request for any additional information about the API when deemed appropriate.
- 6.6. The PRH's responsibility to submit the latest CEP updates, with annexes, as soon as it is available from the API manufacturer.

7. FULL DETAILS OF API INFORMATION IN THE PRODUCT DOSSIER APPLICATION

- 7.1. Information on the *Active pharmaceutical ingredient* sections (ACTD Part II S), including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the product dossier.
- 7.2. The ICH M4Q Technical Guideline and ASEAN Common Technical Requirements (ACTR) provide details on the information to be included in the API sections of an application dossier.
- 7.3. If drug product contains more than one API, the information within Part II S (ACTD) must be provided for each API.
- 7.4. Where the drug substance and the drug product are manufactured by the same company, information on the production, quality control and stability of the drug substance may be submitted as part of the dossier for the drug product (ACTD) rather than in a separate DMF. However, the company is not precluded from submitting a DMF for the drug substance if it prefers to do so.

8. STABILITY DATA OF API

- 8.1. Stability test data for an API should be provided, for at least 3 primary batches. These data should include:
 - Batch details (e.g., batch number, date of manufacture, batch size, use of batch);
 - The general test methodology (e.g., duration of study, storage conditions of temperature and humidity, time points when samples were removed for analysis etc.);
 - The analytical test methods (e.g., assay method of quantitation, determination of degradation products, moisture etc);
 - Validation of test methods;
 - Results of tests; and,
 - Conclusions.
- 8.2. In circumstances where an API retest period has not been established and complete real time stability data is not available at the time of submission, the minimum stability data required are as follows:

- At least 12 months of real time data and 6 months of accelerated data on at least **three** primary batches of the API ;
- The batches should be at least pilot scale-sized and manufactured by a method that simulates the final commercial process.

** In view of this, the re-test date may be extended beyond the end of real time studies which can be extrapolated not more than 12 months covered by the real time data.*

- 8.3. Where the API is sourced from multiple sites, stability data from each site should be provided.
- 8.4. The NPCB may request for additional stability data if deemed necessary for the evaluation of the application.
- 8.5. Stability data is not required where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.

9. SITE INSPECTION

- 9.1. Depending on the outcome of the evaluation of the API dossier, a risk-based approach will be used in the planning of inspections; the approach will take into account the type of APIs as well as the outcome, results and reports of inspections conducted by other regulatory authorities or competent organizations.
- 9.2. The NPCB shall plan and coordinate the performance of inspections at the manufacturing site(s) of the APIs and that of the key intermediate (if relevant) to assess compliance with the relevant sections of the relevant GMP Guidelines, and will compare the technical information on the manufacturing process given in the API dossier shall be compared with the manufacturing process actually carried out on the manufacturing site.
- 9.3. All such inspections shall be performed by inspectors deemed to possess sufficient qualifications and experience in order to perform such inspections, to be competent in areas such as production and quality control of pharmaceuticals, and have appropriate experience in the area of GMP. Such inspectors shall perform the inspections and report on its findings in accordance with established Standard Operating Procedures (SOPs) so as to ensure a standard harmonized approach.

10. MAINTENANCE OF APPROVAL STATUS

10.1. Manufacturers of finished products should establish a mechanism by which manufacturers/ suppliers of an API shall provide information on any changes (i.e., variations) in manufacture and control that may have impact on the safety, purity and quality of the API. It is the PRH's responsibility to provide the NPCB with the appropriate documentation (referring to relevant parts of the dossier) to prove that any intended or implemented variation will not have an impact on the safety, purity and quality of the API that has been previously approved. For those APIs approved by the NPCB, an evaluation of such variations shall be performed with accordance to the ASEAN Variation Guidelines.

10.2. Random samples of APIs supplied to manufacturers of finished pharmaceutical products may be taken for independent testing if there is a need. Certificates of Analysis released by the API manufacturer as well as specifications for test methods shall be provided by the API manufacturer or the PRH to the NPCB for review upon request. In the event of failure to meet the established criteria for testing, the NPCB shall proceed to investigate and communicate this problem to the manufacturer concerned.

10.3. The NPCB may conduct a re-evaluation of the APIs at a 5 year interval. If, as a result of this re-evaluation, it is found that an API and/or specified manufacturing site(s) no longer complies with the recommended standards, such APIs and manufacturing sites will be removed from the approved list. Prior notice to the PRH and API manufacturer shall be issued from the NPCB regarding such decision.

10.4. Re-evaluation may also be done in any situation deemed necessary, including the following:

- If any omissions by the manufacturer in the initial assessment procedure or during the follow-up activities is evident in relation to the requirements. This includes compliance with GMP.
- If any batch(s) of supplied APIs is considered not to be in compliance with the agreed specification of the API;
- If the CEP, or an API for which a CEP dossier was submitted, is cancelled or refused based on the assessment of the dossier for any other reason; and,

- If in the opinion of the NPCB, changes made in the sourcing of key intermediates, route of synthesis, facility or other production, require that reassessment be made.

REFERENCES AND GUIDELINES

a) Guidelines on the Technical Requirements Related to the Quality of Active Pharmaceutical Ingredients

The technical requirements related to the quality of active pharmaceutical ingredients have already been addressed elsewhere, (such as in the ASEAN, WHO, ICH, EDQM and EMA guidelines), and applicants are advised to refer to these guidelines available at the relevant website such as:

- The ASEAN Common Technical Dossier (ACTD) For The Registration Of Pharmaceuticals For Human Use Organization Of The Dossier
(<http://portal.bpfk.gov.my/index.cfm?menuid=46&parentid=15>)
- The Common Technical Document For The Registration Of Pharmaceuticals For Human Use: Quality – M4Q(R1)
(http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf)
- Guideline on Impurities on New Drug Products.
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3B_R2/Step4/Q3B_R2_Guideline.pdf
- Guideline on Impurities in New Drug Substances Q3A
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3A_R2/Step4/Q3A_R2_Guideline.pdf
- Guidelines on Impurities: Guideline For Residual Solvents
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Step4/Q3C_R5_Step4.pdf
- Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part
http://apps.who.int/prequal/info_general/documents/TRS970/TRS_970-Annex4.pdf
- Guideline on Active Pharmaceutical Ingredient Master File (APIMF) Procedure.
(http://apps.who.int/prequal/info_applicants/Guidelines/APIMF_Guide.pdf)

- Guideline on Summary of Requirements for Active Substances. *In The Quality Part of the Dossier.*
(http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002813.pdf)
- Content of the Dossier for Chemical Purity and Microbiological Quality (PA/PH/CEP 04 1 4R)
http://www.edqm.eu/medias/fichiers/Content_of_the_Dossier_for_Chemical_Purity_Microbiological_Quality.pdf
- Content of the Dossier for a Substance for TSE Risk Assessment (PA/PH/CEP (06) 2)
http://www.edqm.eu/medias/fichiers/Content_of_the_Dossier_for_a_Substance_for_TSE_Risk_Assessment.pdf
- Certificates of Suitability for Sterile Active Substances (PA/PH/Exp. CEP/T (06) 13, 1R)
<http://www.edqm.eu/en/New-Applications-29.html>
- Certification database for information on Certificates of Suitability (CEPs) granted by the EDQM.
https://extranet.edqm.eu/publications/recherches_CEP.shtml
- WHO List of Prequalified Active Pharmaceutical Ingredients
http://apps.who.int/prequal/info_applicants/API_PQ-List.htm

b) Guidelines on Stability Testing

The following Guidelines may be consulted in the context of stability testing:

- WHO Technical Report Series, No. 953, 2009 Annex 2: Stability testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products
(http://www.who.int/medicines/publications/pharmprep/PDF_TRS953_WEB.pdf)
- International Conference on Harmonisation. *ICH Q1A (R2): Stability testing of new drug substances and products*
(<http://www.ich.org/LOB/media/MEDIA419.pdf>)
- International Conference on Harmonisation. *ICH Q1B: Photostability testing of new drug substances and products*
(<http://www.ich.org/LOB/media/MEDIA412.pdf>)
- International Conference on Harmonisation. *ICH Q1C: Stability testing of new dosage forms*
(<http://www.ich.org/LOB/media/MEDIA413.pdf>).

- International Conference on Harmonisation. *ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products* (<http://www.ich.org/LOB/media/MEDIA414.pdf>).
- International Conference on Harmonisation. *ICH Q1E: Evaluation for stability data* (<http://www.ich.org/LOB/media/MEDIA415.pdf>).
- Note for Guidance on Stability Testing: Stability Testing Of New Drug Substances And Products (CPMP/ICH/2736/99) (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002651.pdf)
- Note for Guidance *on Stability Testing of Existing Active Substances and Related Finished Products* (www.ema.europa.eu/pdfs/vet/qwp/084699en.pdf)
- ASEAN Stability Guideline (<http://portal.bpfk.gov.my/index.cfm?menuid=46&parentid=15>)

APPENDIX 7:

SPECIAL CONDITIONS FOR REGISTRATION FOR A PARTICULAR PRODUCT OR GROUP OF PRODUCTS

1. BLOOD PRODUCTS

- a) Each batch of the products must comply with WHO requirements for the product.
- b) Each batch of the product imported into Malaysia must be accompanied with a Batch Release Certificate from the relevant authority in the country of manufacture.
- c) Each batch of the product must be accompanied with a certificate confirming that the blood or plasma used in the production of the lot is tested and found to be negative for HIV antibody, HbsAg, HCV and high-risk donors are excluded.
- d) Each batch of the product must be accompanied with a certificate of analysis.

2. ETRETINATE/ ACITRETIN

- a) The product shall only be sold or supplied to:
 - i) Dermatologist (Skin Specialist) who are gazetted with the Ministry of Health, Malaysia, or registered with the Academy of Medicine, Malaysia, and National Specialist Registry;
 - ii) A hospital or Institution maintained by the government, having the services of a skin specialist or registered medical practitioner with experience in dermatology.
- b) The container of the product shall be labeled in a conspicuous and distinct manner, with the following statements:
 - i) "Etretinate/ Acitretin is **highly teratogenic**.
 - ii) Pregnancy must be avoided during treatment and for at least **three years** after **completing** treatment."
- c) A proper record of product supplied stating the product name, product registration number, name, address and contact number of purchaser (prescriber) shall be kept and submitted to the Authority upon request.

- d) The following records shall be maintained for the product and well kept for auditing by the Authority.

Name of Product :			Reg. No :	
Date	Quantity			Name & Address of Purchaser
	Received	Supplied	Balance	
Name and Address of : Importer/Manufacturer/Wholesaler : Import/Manufacturer's/Wholesaler's Licence No :				

3. HUMAN GROWTH HORMONE (Somatotropin, Somatropin)

A proper record of product supplied stating the product name, product registration number, name, address and contact number of purchaser (prescriber) shall be kept and submitted to the Authority upon request.

4. ISOTRETENOIN/ TRETINOIN

- a) The product shall only be sold or supplied to:
- Dermatologist (Skin Specialist) who are gazetted with the Ministry of Health, Malaysia, or registered with the Academy of Medicine, Malaysia, and National Specialist Registry.
 - A hospital or institution maintained by the government, having the services of a skin specialist or registered medical practitioner with experience in dermatology.
- b) The container of the product shall be labelled in a conspicuous and distinct manner, with the following statements:
- "Isotretinoin/ tretinoin is **highly teratogenic**.
 - Pregnancy must be avoided during treatment and for at least **1 month** after **completing** treatment."

- c) A proper record of product supplied stating the product name, product registration number, name, address and contact number of purchaser (prescriber) shall be kept and submitted to the Authority upon request.

5. MIDAZOLAM

Products containing midazolam are restricted for use in government and private hospitals and specialist clinics only.

6. PARACETAMOL IN COMBINATION WITH CAFFEINE

- a) For products containing a combination of paracetamol and caffeine, dose unit of caffeine for adults is 65mg and maximum dose of caffeine is 520mg per day, meanwhile, dose unit for paracetamol is 500mg with the maximum dose of 4,000mg per day or 8 tablets daily.
- b) Products containing caffeine for pediatrics are not allowed.
- c) Allowable packing size should not exceed 20 tablets/ capsules.

7. VACCINES

- a) Each batch of the product must comply with WHO requirements for the product.
- b) Each batch of the product imported into Malaysia must be accompanied with a batch release certificate.

APPENDIX 8:

LIST OF PERMITTED, PROHIBITED AND RESTRICTED SUBSTANCES

IMPORTANT NOTES:

The following lists are by no means exhaustive.

Outline:

8.1 List of Prohibited and Restricted Active Ingredients and Combination

8.1.1 List of Prohibited Active Ingredients and Combinations

- a) Specific Active Ingredients
- b) Combinations

8.1.2 List of Restricted Active Ingredients and Combinations

- a) Specific Active Ingredients
- b) Combinations

8.2 List of Prohibited and Restricted Excipients

8.2.1 List of Prohibited Excipients

8.2.2 List of Restricted Excipients

8.3 List of Permitted and Restricted Colouring Agents

8.3.1 List of Permitted Colouring Agents

8.3.2 List of Restricted Colouring Agents

8.1 LIST OF PROHIBITED AND RESTRICTED ACTIVE INGREDIENTS AND COMBINATION

8.1.1 LIST OF PROHIBITED ACTIVE INGREDIENTS AND COMBINATIONS

a) Prohibited Active Ingredients

NO.	PROHIBITED ACTIVE INGREDIENTS
1.	1,3-dimethylamylamine (DMAA)
2.	Aristolochic Acid
3.	Aminopyrine/ Amidopyrine
4.	Astemizole
5.	Bacillus Coagulans
6.	Berberine
7.	Butobarbitone
8.	Chlormezanone
9.	Cisapride
10.	Conjugated Linoleic Acid
11.	Crinis Carbonisatus
12.	Danthron
13.	Dipyrone
14.	Enterococcus Faecalis
15.	Enterococcus Faecium
16.	Ethenzamide
17.	Euflavine
18.	Furazolidone
19.	Fenfluramine/ Dexfenfluramine
20.	Gentian Violet
21.	Gamma-Butyrolactone (GBL)

NO.	PROHIBITED ACTIVE INGREDIENTS
22.	Gamma-Hydroxybutyric Acid (GHB)
23.	Haloquinol
24.	Hexachlorophene
25.	Mercurochrome
26.	Nimesulide
27.	Novobiocin
28.	Oxyphenisatin Acetate/ Acetophenolisatin
29.	Oxyphenbutazone
30.	Pergolide
31.	Phenacetin
32.	Phenazone/ Antipyrine <ul style="list-style-type: none"> - Propylphenazone - Isopropylphenazone
33.	Phenylbutazone
34.	Phenylpropalamine
35.	Piperazine
36.	Prenylamine
37.	Quinalbarbitone
38.	Salicylamide
39.	Sibutramine
40.	Stanozolol
41.	Sulphaguanide
42.	Thioridazine
43.	Tegaserod
44.	Terfenadine

b) Prohibited Combinations

NO.	PROHIBITED COMBINATIONS
1.	Ampicillin + Cloxacillin
2.	Antibiotics + Papain/ Prolase
3.	Antacid + Charcoal
4.	Combinations With Any Barbiturates
5.	Combinations of Two or More Analgesic with the Same Mode of Action
6.	Combinations Of Vitamin (S) With Other Drugs: <ol style="list-style-type: none"> Vitamin (S) + Appetite Suppressant Vitamin (S) + Corticosteroid Vitamin (S) + Analgesic Vitamin (S) + Laxative Vitamin (S) + Slimming Agents
7.	Cough, Cold and Allergy Products Containing: <ol style="list-style-type: none"> Four or More Pharmacological Groups in One Product. Two or More Drugs from the Same Pharmacological Group Antipyretic - Analgesic + Expectorant Anticholinergic + Bronchodilator Codeine + Ephedrine/ Pseudoephedrine Methapyrilene Paracetamol + Mucolytic/ Expectorant
8.	Combinations Containing Antacid and Surface Local Anaesthetic Agent
9.	Combinations Containing Dextropropoxyphene
10.	Combinations Containing Spironolactone
11.	Corticosteroids + Antihistamines
12.	Eye Drops Containing Vitamin
13.	Gripe Water Containing Alcohol
14.	Propanolol + Hydralazine

NO. PROHIBITED COMBINATIONS

- | | |
|-----|--|
| 15. | Propanolol + Spironolactone |
| 16. | Topical Preparation Containing Combination of Antibiotic, Antifungal and Steroid |

8.1.2 LIST OF RESTRICTED ACTIVE INGREDIENTS AND COMBINATIONS

Specific Active Ingredients	Not Allowed in the Specified Preparation(s) or Condition
1. Acetic Acid	Expectorant
2. Allantoin	Eye Drop
3. Allergen Extracts	Vaccines, Diagnostics
4. Amphetamine	Cough Mixtures, Appetite Suppressants
5. Animal Organ	All Preparations Except Natural Products
6. Antihistamine	Topical Use
7. Bismuth Salts Except Bismuth Subcitrate	Oral Preparations
8. Boric Acid/ Borax And Related Salts	Oral, Topical (Skin), Vaginal, Nasal Dosage Form
9. Buprenorphine	Single Active Ingredient Sublingual Tablet Formulation
10. Caffeine	All Preparations Except for an Oral Preparation in Combination with Paracetamol/ Acetaminophen or Combination with Ergotamine
11. Camphor	- Oral - External (>11%)
12. Chloroform	Expectorant
13. Codeine	Cough Syrup
14. Cocillana Liq. Extract	Expectorant
15. Cyproheptadine	Appetite Stimulant
16. Dextromethorphan	Single Active Ingredient in Tablet Form,

	including lozenges
17. Dihydrostreptomycin	Oral Antidiarrhoeals
18. Diphenoxylate	Liquid Oral Dosage For Anti-Diarrhoeal
19. Quinestrol, Oestrogen	Lactation Suppressant
20. Ethynodiol Diacetate	Oral Contraceptives
21. Euphorbia Liquid Extract	Expectorant
22. Gatifloxacin	All Preparations Except for Eye Drop
23. Germanium	Non Naturally Occurring
24. Hydroquinone	Oral
25. Lactobacillus Acidophilus	Antidiarrhoeal
26. Loperamide	Liquid Oral Dosage For Anti-Diarrhoeal
27. Lovastatin	In Red Yeast Rice: > 1 % w/w and > 10mg/Day
28. Lynooestrenol	Oral Contraceptives
29. L-Tryptophan	All Preparations Except Parenteral Nutrition Products And Enteral Feeding Products
30. Magnesium Ascorbryl Phosphate	Antipigmentation
31. Menthol	External Preparations >16%
32. Mestranol	Oral Contraceptives
33. Methylene Blue	Oral Preparations
34. Midazolam	All oral preparations, except 7.5mg coated tablet
35. Morphine	Cough Mixtures
36. Neomycin	Oral Antidiarrhoeal, Vaginal Tablets, Topical Powders, Aerosols, Nasal Preparations
37. Noradrenaline	Dental Preparations
38. Norgestrel	Oral Contraceptives
39. Paracetamol	Liquid Oral 500mg/5ml
40. Penicillin	Topical Use
41. Phenazopyridine	Urinary Analgesics
42. Phenolphthalein	Stimulant Purgative
43. Pizotifen	Appetite Suppressant

44. Podophyllum Resin	Oral Preparations
45. Pseudoephedrine	All Single Active Ingredient Formulations
46. Sulphonamides	Topical Use
47. Sulphur	All preparations Except External Preparation
48. Squill	Expectorant
49. Terpene Hydrate	Expectorant
Combinations	Not Allowed in the Specified Preparation(s)
1. Cough, Cold And Allergy Products Containing:	
i) Antimony Potassium Tartrate	Expectorant
ii) Allylisothiocyanate/ Mustard Oil	Nasal Decongestant
iii) Turpentine Oil	Expectorant/ Antitussive
2. Vitamin(s)	Eye Drops

8.2 LIST OF PROHIBITED AND RESTRICTED EXCIPIENTS

8.2.1 LIST OF <u>PROHIBITED EXCIPIENTS</u>	8.2.2 LIST OF <u>RESTRICTED EXCIPIENTS</u>	
	Excipients	Restrictions
1. Colouring Agents (Including in Capsule Shells)	1. Colouring Agents (Including in Capsule Shells)	
a) Amaranth (CI= 16185, FD & C Red No. 2, E123)	a) Tartrazine (CI= 19140, FD & C Yellow No.5, E102)	Not allowed in the following preparations: - Oral; - Rectal; - Vaginal or - Nasal Preparations
	b) Red 2G	Not allowed in the following preparations: - Oral Preparations; and - Preparations Used for Mucosa Membrane
2. Others	2. Sweeteners/ Flavouring Agent	
a) Chlorofluorocarbons (CFC) b) Dibutyl Pthalate	a) Menthol	Limited to not more than 10mg/day
	b) Saccharin and Salts	Limited to not more than 5mg/kg/day
	c) Cyclamates	Limited to not more than 1.5mg/kg body weight/day
	3. Preservatives	
	a) Chloroform	Limited to not more than 0.5% in Pharmaceuticals for Internal Use
	b) Thiomersal *	Not allowed in ophthalmic Preparations

* For other preparations, warning as specified in [Appendix 9: Labelling Requirement](#), shall be included in the package insert and product literature of products containing thiomersal.

Additional Information

1. **Methylene Chloride/ Dichloromethane** are not allowed as solvent in film-coating for locally manufactured products.

For detail on implementation, please refer circular [\(2\)dIm.BPFK/30/06/2 Bhgn 2.](#)

2. **Alcohol** is not allowed unless it is essential to the formulation and no suitable alternatives to alcohol are available. Content of alcohol shall be at the minimum level as possible.

8.3 LIST OF PERMITTED AND RESTRICTED COLOURING AGENTS

8.3.1 List of Permitted Colouring Agents

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
1.	Allura Red AC/ FD & C Red No.40	16035
2.	Anthocyanins a. Those glycosides of 2-phenylbenzopyrylium salts which are anthocyanins b. The following anthocyanidin aglycones : i. Pelargonidin ii. Cyanidin iii. Peonidin iv. Delphinidin v. Petunidin vi. Malvidin	
3.	Black PN (Brilliant Black BN)	28440
4.	Brilliant Blue FCF	42090
5.	Calcium Carbonate	
6.	Carbo Medicinals/ Vegetalis; (Charcoal)	
7.	Caramel	
8.	Carmoisine (or Azorubine)	14720
9.	Carotenoids a. Alpha, Beta, Gamma-Carotene b. Bixin, Noribixin, Roucou c. Annatto d. Capsanthin, Capsorubin, (paprika extract) e. Lycopene f. Beta-Apo-8' carotenal (C 30) g. Ethyl ester of Beta-Apo-8 Carotenoic Acid (C30) i. Chlorophyll ii. Copper complexes of Chlorophyll and Chlorophyllins	75120 40820 75810
10.	Chocolate Brown HT	20285
11.	Cochineal or Carminic Acid, Carmine from Cochineal	75470
12.	Curcumin	75300
13.	Fast Green FCF (FD & C Green No.3)	42053

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
14.	Green S (Acid Brilliant Green BS, Lissamine Green)	
15.	Indigo Carmine (Indigotine)	73015
16.	Lactoflavin, Riboflavin	
17.	Patent Blue V	42051
18.	Ponceau 4R (Cochineal Red A)	16255
19.	Quinoline Yellow	47005
20.	Xanthophylls a. Flavoxanthin b. Lutein c. Cryptoxanthin (Kryptoxanthin) d. Violoxanthin e. Rhodoxanthin f. Canthaxanthin	40850
21.	The Following Colouring Matters Natural to Edible Fruits or Vegetables: a. Alkannin b. Annatto (including eye) c. Carotene (including eye) d. Chlorophyll e. Flavine f. Indigo g. Osage h. Orange i. Persian Berry j. Safflower k. Saffron l. Sandalwood m. Turmeric n. or their pure coloring principles whether isolated from such natural colors or produced synthetically	75530
22.	Bole or Iron Oxide, Carbon Black (or Vegetable Origin), Titanium Dioxide	77891
23.	The Aluminium Salts (Lakes) of Any of the Scheduled Synthetic Dyes Approved for Use, (a) Alumina (Dried Aluminium Hydroxide)	
24.	Talc	

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
25.	Indigo Carmine/ FD & C Blue No. 2	73015
26.	Brilliant Blue FCF Ammonium Salt/ D & C Blue No. 4	42090
27.	Alizarin Cyanine Green F/ D & C Green No. 5	61570
28.	Toney Red/ D & C Red No. 17	26100
29.	Eosin YS Acid Form/ D & C Red No. 21	45380:2
30.	Eosinys Sodium Salt/ D & C Red No. 22	45380
31.	Phloxine B Acid Form/ D & C Red No. 27	45410:1
32.	Phloxine B Sodium Salt/ D & C Red No. 28	45410
33.	Helindone Pink CN/ D & C Red No. 30	73360
34.	Erythrosine/FD & C Red No. 3	45430
35.	Yellow 2G (Food Yellow)	
37.	Orange Yellow S Sunset Yellow FCF (FD & C Yellow No. 6, E110)	15985

8.3.2 List of Restricted Colouring Agents

The following colouring agents are **ALLOWED** in preparations as stated in the parentheses:

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
1.	Dihydroxyacetone (external use with specific drugs only)	
2.	Bismuth Oxychloride (external use only, including eye)	77163
3.	Ferric Ammonium Ferrocyanide (external use only, including eye)	
4.	Ferric Ferrocyanide (external eye only)	
5.	Chromium Hydroxide Green (external use only)	77289
6.	Chromium Oxide Green (external use only, including eye)	
7.	Guanine (external use only)	75170
8.	Prophyllite (external use only)	
9.	Mica (external use only, including eye)	77019
10.	Bronze (external use only, including eye)	
11.	Copper (external use only, including eye)	
12.	Zinc Oxide (external use only, including eye)	77947
13.	Quinizarine Green SS/ D & C Green No. 6 (external use only)	61565
14.	Pyranine Concentrated/ D & C Green No. 8 (external use only)	59040
15.	Orange II/ D & C Orange No. 4 (external use only)	15510

NO.	COLOURING AGENTS	COLOUR INDEX NUMBER (CI)
16.	Dibromofluorescein/ D & C Orange No. 5 (mouth wash, dentifrices, external use only)	45370
17.	Diiodofluorescein/ D & C Orange No. 10 (external use only)	45425
18.	D & C Orange No. 11 (external use only)	
19.	Ponceau SX/ FD & C Red No. 4 (external use only)	14700
20.	Lithol Rubin B/ D & C Red No. 6 (may be use in combination; total not more than 5mg/day)	15850
21.	Lithol Rubin B CA/ D & C Red No. 7 (may be used in combination; total not more than 5mg/day)	15850:1
22.	D & C Red No. 31 (external use only)	
23.	Deep Maroon/ D & C Red No. 34 (external use only)	15880:1
24.	D & C Red No. 39 (external use only, not more than 0.1%)	
25.	Uranine Acid Form/ D & C Yellow No. 7 (external use only)	45350:1
26.	EXT. D & C Yellow No. 7 (external use only)	
27.	Uranine Sodium Salt/ D & C Yellow No. 8 (external use only)	45350
28.	Tartrazine/ FD & C Yellow No. 5/MA Yellow A-2/ Aluminic Lake (external use only)	19140

APPENDIX 9:

LABELLING REQUIREMENTS

This appendix comprises of two (2) parts:

a) General Labelling Requirements for:

- i) Section D : Label (Mock-Up) for Immediate Container and Outer Carton
- ii) Section D : Proposed Package Insert (PI)
- iii) Section E8/ F8 : Patient Information Leaflet (PIL)

b) Specific Labelling Requirements

9.1 GENERAL LABELLING REQUIREMENTS

9.1.1 LABEL (MOCK-UP) FOR IMMEDIATE CONTAINER AND OUTER CARTON

The following information in **Table 1** shall present on the label of a product at outer carton, immediate container or blister/ strips:

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
1.	Product Name	✓	✓	✓
2.	Dosage Form	✓	✓*	NA
3.	Name of Active Substance(s)	✓	✓	✓**
4.	Strength of Active Substance(s)	✓	✓	✓**
5.	Batch Number	✓	✓	✓
6.	Manufacturing Date	✓	✓*	NA
7.	Expiry Date	✓	✓	✓
8.	Route of Administration	✓	✓	NA
9.	Storage Condition	✓	✓*	NA
10.	Country's Registration Number	✓	✓*	NA
11.	Name & Address of Product Registration Holder (PRH)	✓	✓*	Name/ Logo of Manufacturer/ Product Owner
12.	Name & Address of Manufacturer	✓ At least name of town/ city and country of manufacturer	✓* At least name of town/ city and country of manufacturer	NA
13.	Warnings and/or Specific Labelling (if applicable)	✓	✓*	NA
14.	Pack Sizes (unit/ volume)	✓	✓	NA
15.	Name & content of preservative(s) where present	✓	✓	NA

No.	Parameters	Outer Carton (Unit Carton)	Immediate Labels	Blister/ Strips
16.	Name & content of alcohol, where present	✓	✓	NA
17.	To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine (capsule shell).	✓	✓	NA
18.	Recommended daily allowance (RDA) for vitamins/ multivitamins/ mineral preparations used as dietary supplements	✓	✓	NA
19.	The words “Keep medicine out of reach of children” or words bearing similar meaning in both <i>Bahasa Malaysia</i> & English	✓	✓*	NA
20.	Other country specific labelling requirements (if applicable)	✓	✓*	NA
21.	The words “Controlled Medicine”/ “ <i>Ubat Terkawal</i> ” (For scheduled poison only)	✓	✓*	NA
22.	Security Label (Hologram)	✓ #	✓*	NA

NA : Not Applicable

* Exempted for small labels (i.e. 5ml and less) used for ampoules/ cartridge, vials, eye drops, ear drops, and nose drops.

** For multi-vitamins and minerals preparations it is suggested to label as multi-vitamins and minerals.

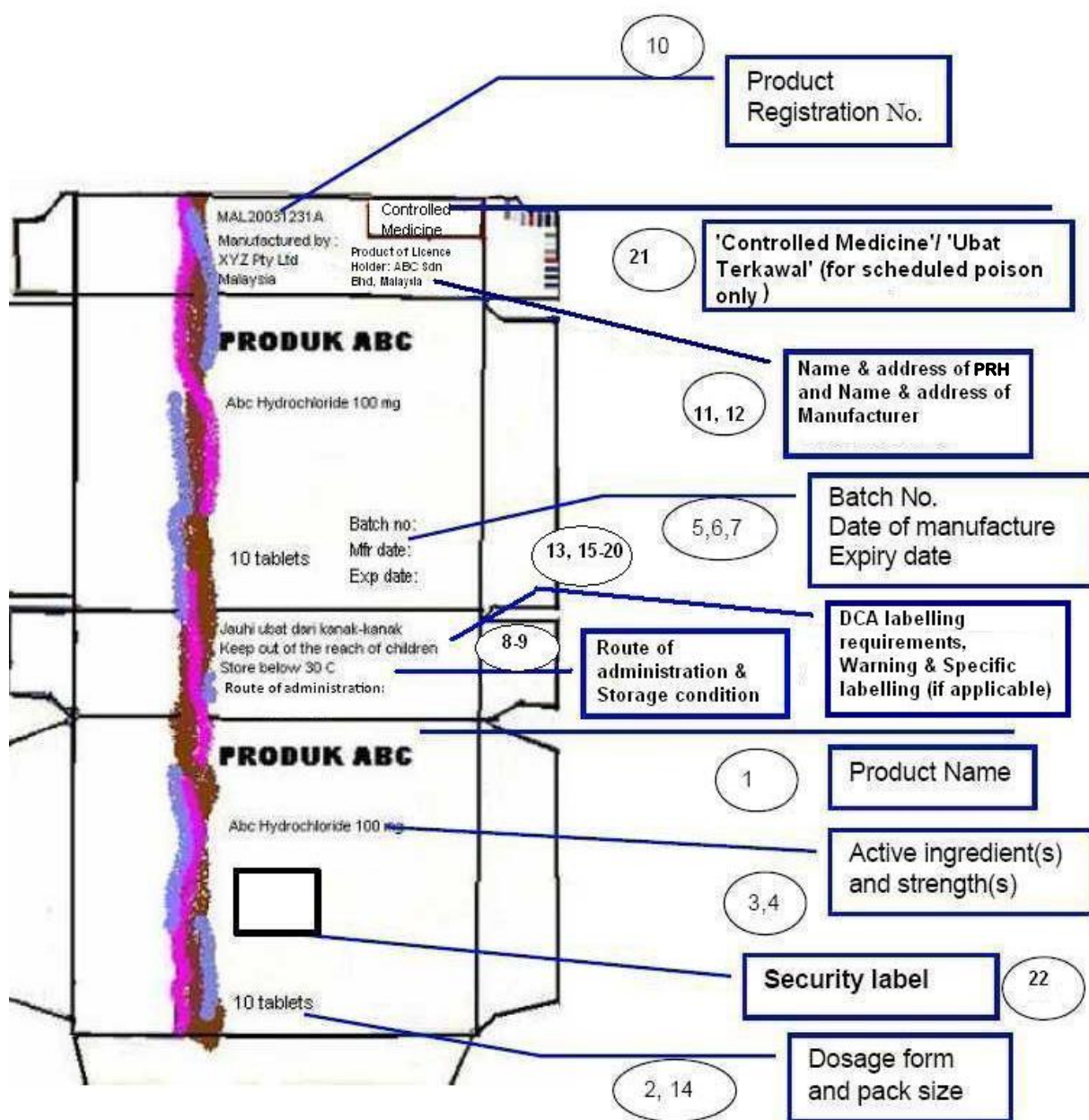
In case of no outer carton, the security label shall be applied to the immediate labels. The security label shall not be applied onto outer shrink wrap of a product.

No. 15, 19, 21 & 22 of the above are country specific requirements for Malaysia.

Additional Information:

- a) If the product is without an outer carton, the inner label shall bear all the information that is required.
- b) Official website of the company or website for any purpose of product promotion from the PRH/ product owner/ manufacturer is not allowed to be printed on the product label (applicable to all categories of products inclusive of imported products). However, the email address of the company is permissible on the label.
- c) The colours of labels shall be differentiated between strengths of products as well as between products containing different active ingredients which belong to the same holder.
- d) Only a single label artwork is permitted for all pack sizes of a registered product.
- e) No stick-on label is permitted. Any usage of stick-on label shall have prior approval by the Authority. The Authority will only consider the following situations:
 - i) Stick-on label of such information and printing of registration number for label redressing of a registered product is permitted:

Words with “Controlled Medicine”/ *Ubat Terkawal*, *Jauhi daripada kanak-kanak*, information of Product Registration Holder, Malaysia Specific Labelling Requirements shall be printed in a single label.
 - ii) The label shall be made from good quality material and not easy to be torn out.
 - iii) However, registration number shall be printed permanently on the product (ink-jet) and it is not allowed to be printed on the stick-on label.
- f) Use of QR code is permitted only for the purpose of monitoring inventory of the product, such as batch number, expiry date and manufacturing date, BUT NOT for linkage to any website. The addition of QR code on registered product labels without variation approval from NPCB can be considered only if that is the only proposed change to the currently approved labels.
- g) Please refer to **Figure 1** as an example of a product label which in accordance to the labelling requirements.

Figure 1:**Note:**

Numerical notations shown in the above figure are in line with the numbering for the parameters, shown in Table 1 above, to be included in the product label (as identified and adopted by the ACCSQ-PPWG).

9.1.2 PROPOSED PACKAGE INSERT

Package insert (PI) is required for products containing scheduled poison and for injectable OTC products. PI may also be submitted for other OTC products. The draft copy of the PI shall be submitted for evaluation.

Sharing of PI is only allowed for products having the same active ingredient(s) but with different strengths.

The following information is required to be included in the PI:

- a) Brand or Product Name
- b) Name and Strength of Active Substance(s)
- c) Product Description
- d) Pharmacodynamics/ Pharmacokinetics
- e) Indication
- f) Recommended Dosage
- g) Route of Administration
- h) Contraindications
- i) Warnings and Precautions
- j) Interactions with Other Medicaments
- k) Statement on usage during pregnancy and lactation
- l) Adverse Effects/ Undesirable Effects
- m) Overdose and Treatment
- n) Incompatibilities (For injections only)
- o) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
- p) Dosage forms and packaging available
- q) Name and address of manufacturer/ product registration holder
- r) Date of revision of PI

9.1.3 PATIENT INFORMATION LEAFLET

Patient Information Leaflet (PIL) or in *Bahasa Malaysia* known as *Risalah Maklumat Ubat Pesakit (RiMUP)*, is compulsory for products which are self-administered by patients, including:

- a) Scheduled poisons (Category A);
- b) Over-the-Counter, OTC products (Category X);
- c) Health supplements with high claims (disease risk reduction).

For details, please refer to:

- i) *Direktif Penguatkuasaan Keperluan Mengemukakan Risalah Maklumat Ubat untuk Pengguna (RiMUP) Bil. 5 Tahun 2011* [Bil \(15\) dlm BPFK/PPP/01/03 Jld 1](#)
- ii) [Garis panduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna \(RiMUP\)](#)

The draft copy of the PIL in both English and *Bahasa Malaysia* shall be submitted for evaluation.

Note:

PIL is not compulsory to be sold with the product but will be uploaded onto NPCB website as reference for patients or consumers.

For OTC Products, if the product is intended to be sold without a PI or PIL, the information required to be included in the PI or PIL shall be printed on the unit outer-carton of the product.

9.2 SPECIFIC LABELLING REQUIREMENTS

Please refer Table 2: List of Substances Which Requires Specific Labelling Requirements and Table 3: Details of Specific Labelling Requirements.

Table 2: List of Substances Which Requires Specific Labelling Requirements:

NO.	SUBSTANCES
1.	5-ALPHA REDUCTASE INHIBITOR (5-ARI)
2.	ACE INHIBITORS
3.	ACETYLSALICYLIC ACID (ASPIRIN)
4.	ACTIVATED CHARCOAL/ ATTAPULGITE
5.	ALBENDAZOLE & BENZIMIDAZOLE ANTIHELMINTICS
6.	ALFALFA (<i>MEDICO SATIVA</i>)
7.	ALLOPURINOL
8.	ALPHA DIHYDROERGOCRYPTINE
9.	ALPRAZOLAM
10.	AMIODARONE
11.	ANTIDEPRESSANTS
12.	ANTIEPILEPTICS
13.	ANTIPSYCHOTIC AGENTS
14.	APOMORPHINE
15.	ARGININE
16.	ARIPIRAZOLE
17.	ASPARTAME
18.	BEE POLLEN
19.	BENZOYL PEROXIDE
20.	BENZYL ALCOHOL
21.	BLACK COHOSH (<i>CIMICIFUGAE RACEMOSAE</i>)

NO.	SUBSTANCES
22.	BROMAZEPAM
23.	BROMOCRIPTINE
24.	BROMPHENIRAMINE
25.	CAMPHOR
26.	CARBAMAZEPINE
27.	CARBIMAZOLE
28.	CABERGOLINE
29.	CEFTRIAZONE
30.	CETIRIZINE
31.	<i>CHELIDONIUM MAJUS</i>
32.	CHITOSAN
33.	CHLORPHENIRAMINE
34.	CHORIONIC GONADOTROPHIN
35.	CLEMASTINE
36.	CLINDAMYCIN
37.	CLOBAZAM
38.	CLOPIDOGREL
39.	CLOZAPINE
40.	COLCHICINE
41.	COX-2 INHIBITORS
42.	CYPROTERONE ACETATE
43.	CYTOTOXIC AGENT
44.	DEXBROMPHENIRAMINE
45.	DEXTROMETHORPHAN
46.	DIAZEPAM

NO.	SUBSTANCES
47.	DICLOFENAC SODIUM
48.	DICYCLOMINE
49.	DIPHENHYDRAMINE
50.	DIPHENOXYLATE
51.	DOPAMINERGIC INGREDIENT
52.	EPHEDRINE
53.	FAMOTIDINE
54.	FIBRATES
55.	FLUCLOXACILLIN
56.	FLUORIDE
57.	FLUOROQUINOLONES
58.	FLURAZEPAM HYDROCHLORIDE
59.	GADOBENIC ACID
60.	GADOBUTROL
61.	GADODIAMIDE
62.	GADOLINIUM OXIDE
63.	GADOTERIC ACID
64.	GADOVERSETAMIDE
65.	GADOXETIC ACID
66.	GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
67.	GENTAMICIN TOPICAL PREPARATIONS
68.	GINKGO BILOBA/ GINKGO EXTRACT
69.	GINSENG
70.	GLUCOSAMINE
71.	HIV PROTEASE INHIBITORS

NO.	SUBSTANCES
72.	HYDROQUINONE
73.	IMMUNOSUPPRESANTS
74.	INSULIN
75.	INGREDIENTS DERIVED FROM SEAFOOD
76.	KAOLIN, PECTIN, KAOLIN-PECTIN
77.	KETOCONAZOLE
78.	KETOROLAC TROMETHAMOL (KETOROLAC TROMETHAMINE)
79.	LEVODOPA
80.	LINCOMYCIN
81.	LISURIDE
82.	LIQUID PARAFFIN
83.	LOPERAMIDE
84.	LORATADINE
85.	LORAZEPAM
86.	METHYL SALICYLATE
87.	METHYLPHENIDATE HCL
88.	METOCLOPRAMIDE
89.	MICONAZOLE
90.	MIDAZOLAM
91.	MINOXIDIL
92.	MUCOLYTIC AGENT
93.	NEVIRAPINE
94.	NIFEDIPINE
95.	NITRATES
96.	NITRAZEPAM

NO.	SUBSTANCES
97.	NORFLOXACIN
98.	NORMAL GLOBULIN
99.	NOSCAPINE
100.	NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)
101.	OLANZAPINE
102.	PARACETAMOL
103.	PARACETAMOL WITH CAFFEINE IN COMBINATION
104.	<i>PELARGONIUM SIDOIDES</i>
105.	PENICILLIN
106.	PHENIRAMINE
107.	PHENYLEPHRINE
108.	PIRIBEDIL
109.	PIROXICAM
110.	PRAMIPEXOLE
111.	PROMETHAZINE HCL
112.	PROPAFENONE
113.	PROPOFOL
114.	PROPOLIS (TOPICAL)
115.	PROPYLTHIOURACIL
116.	PSEUDOEPHEDRINE
117.	PSYCHOTROPIC PRODUCTS
118.	QUETIAPINE
119.	QUINAGOLIDE
120.	RISPERIDONE
121.	ROPIRINOLE

NO.	SUBSTANCES
122.	ROSIGLITAZONE
123.	ROYAL JELLY
124.	SALBUTAMOL
125.	SEDATIVE – HYPNOTIC PRODUCTS
126.	SELENIUM SULPHIDE
127.	SENNA LEAF (CASSIA) AND RHUBARB/ RADIX <i>et</i> RHIZOMA RHEI
128.	SODIUM METABISULPHITE (EXCIPIENT)
129.	SODIUM VALPROATE
130.	ST. JOHN'S WORT (<i>Hypericum perforatum</i>)
131.	STATINS
132.	SULPHONAMIDES/ TRIMETHOPRIM
133.	TERBUTALINE
134.	TETRACYCLINE SYRUP
135.	THIOMERSAL
136.	THROMBOLYTIC AGENTS
137.	TIAPROFENIC ACID
138.	TRETINOIN (TOPICAL)
139.	TRIAZOLAM
140.	TRIMETAZIDINE
141.	TRIPROLIDINE
142.	VARENICLINE
143.	VITAMIN K
144.	WARFARIN
145.	ZIPRASIDONE
146.	ZOLPIDEM TARTRATE

NO.	SUBSTANCES
147.	ZOPICLONE

Table 3: Details of Specific Labelling Requirements

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
1.	<p data-bbox="277 371 919 409"><u>5-ALPHA REDUCTASE INHIBITOR (5-ARI)</u></p> <p data-bbox="277 434 1407 506">The following statement shall be <u>included in the package inserts</u> of products containing 5-ARI:</p> <p data-bbox="277 544 1011 582"><u>1.1 PRODUCT CONTAINING FINASTERIDE 5MG</u></p> <p data-bbox="336 618 839 651">WARNINGS AND PRECAUTIONS</p> <p data-bbox="336 678 1046 714">Increased Risk of High-Grade Prostate Cancer</p> <p data-bbox="336 739 1407 994">Men aged 55 and over with a normal digital rectal examination and PSA ≤ 3.0 ng/mL at baseline taking finasteride 5 mg/day in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (dutasteride, AVODART) (1% dutasteride vs 0.5% placebo).</p> <p data-bbox="336 1021 1407 1164">5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.</p> <p data-bbox="336 1202 831 1236">Increased Risk of Breast Cancer</p> <p data-bbox="336 1263 1407 1411">Breast cancer has been reported in men taking finasteride 5 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.</p> <p data-bbox="336 1449 1158 1482">ADVERSE EVENTS: POST MARKETING EXPERIENCE</p> <p data-bbox="336 1509 616 1543">Male breast cancer</p> <p data-bbox="277 1615 1011 1653"><u>1.2 PRODUCT CONTAINING FINASTERIDE 1MG</u></p> <p data-bbox="336 1688 839 1722">WARNINGS AND PRECAUTIONS</p> <p data-bbox="336 1749 1046 1785">Increased Risk of High-Grade Prostate Cancer</p> <p data-bbox="336 1809 1407 2027">Men aged 55 and over with a normal digital rectal examination and PSA ≤ 3.0 ng/mL at baseline taking finasteride 5 mg/day (5 times the dose of [Brand Name]) in the 7-year Prostate Cancer Prevention Trial (PCPT) had an increased risk of Gleason score 8-10 prostate cancer (finasteride 1.8% vs placebo 1.1%). Similar results were observed in a 4-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p>(dutasteride, AVODART) (1% dutasteride vs 0.5% placebo).</p> <p>5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.</p> <p>Increased Risk of Breast Cancer</p> <p>Breast cancer has been reported in men taking finasteride 1 mg during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps, pain, gynaecomastia or nipple discharge.</p> <p>ADVERSE EVENTS: POST MARKETING EXPERIENCE</p> <p>Male breast cancer</p> <p>1.3 <u>PRODUCT CONTAINING DUTASTERIDE</u></p> <p>WARNINGS AND PRECAUTIONS</p> <p>Increased Risk of High-Grade Prostate Cancer</p> <p>In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and 10.0 ng/mL taking AVODART in the 4-year Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, there was an increased incidence of Gleason score 8-10 prostate cancer compared with men taking placebo (AVODART 1.0% versus placebo 0.5%). In a 7-year placebo-controlled clinical trial with another 5-alpha reductase inhibitor (finasteride 5 mg, PROSCAR), similar results for Gleason score 8-10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%).</p> <p>5-alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5-alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.</p> <p>Reference:</p> <ul style="list-style-type: none"> a) Circular Bil (19) dlm BPFK/PPP/01/03 Jld 1: Direktif untuk Memuatkan Kenyataan Amaran Berkaitan dengan Risiko High-Grade Prostate Cancer dalam Sisip Bungkusan Semua Produk 5-Ari b) Circular Bil (64) dlm BPFK/PPP/01/03 Jld 1: Direktif untuk Memuatkan Kenyataan Amaran Berkaitan dengan Risiko Kanser Payudara Di Kalangan Pesakit Lelaki dalam Sisip Bungkusan Semua Produk Yang Mengandungi Finasteride

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
2.	<p><u>ACE INHIBITORS</u></p> <p>The following statement shall be <u>included in the package inserts</u> of products containing ACE inhibitors:</p> <p>WARNING</p> <ul style="list-style-type: none"> • INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY <p>USE IN PREGNANCY</p> <ul style="list-style-type: none"> • INCREASED RISK OF BIRTH DEFECTS, FOETAL AND NEONATAL MORBIDITY AND DEATH WHEN USED THROUGHOUT PREGNANCY <p><i>Reference: Circular Bil (65) dlm BPFK/02/5/1.3: Produk yang Mengandungi 'ACE Inhibitors'</i></p>
3.	<p><u>ACETYLSALICYLIC ACID (ASPIRIN)</u></p> <p>For products containing Acetylsalicylic acid, the following <u>warning shall be included on the labels</u> in two languages (<i>Bahasa Malaysia</i> and English):</p> <p>AMARAN TIDAK BOLEH DIBERI KEPADA KANAK-KANAK BERUMUR KURANG DARIPADA 16 TAHUN.</p> <p>WARNING NOT TO BE GIVEN TO CHILDREN UNDER 16 YEARS OF AGE.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
4.	<p><u>ACTIVATED CHARCOAL/ ATTAPULGITE</u></p> <p>4.1 The following <u>boxed warning</u> shall be <u>included on the labels</u> of products containing Activated charcoal/ attapulgite:</p> <div data-bbox="336 461 1378 562" style="border: 1px solid black; padding: 5px; text-align: center;"> NOT RECOMMENDED FOR TREATMENT OF DIARRHOEA IN CHILDREN UNDER 6 YEARS OF AGE </div> <p>4.2 The following <u>statements</u> shall be <u>included in the package inserts</u> of products containing Activated charcoal/ attapulgite:</p> <div data-bbox="336 707 1378 808" style="border: 1px solid black; padding: 5px; text-align: center;"> Not recommended for treatment of diarrhoea in children under 6 years of age </div> <p>WARNING Activated charcoal/ attapulgite may interfere with the absorption of other drugs, including antibiotics, when administered concurrently.</p> <p>PRECAUTION Appropriate fluid and electrolyte therapy should be given to protect against dehydration. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative.</p>
5.	<p><u>ALBENDAZOLE & BENZIMIDAZOLE ANTIHELMINTICS</u></p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of products containing Albendazole or Benzimidazole antihelmintics:</p> <p>SHOULD NOT BE ADMINISTERED DURING CONFIRMED OR SUSPECTED PREGNANCY</p>
6.	<p><u>ALFALFA (MEDICO SATIVA)</u></p> <p>The following <u>boxed warning</u> shall be <u>included on the labels</u> of products containing Alfalfa (<i>Medico sativa</i>):</p> <div data-bbox="331 1805 1378 1973" style="border: 1px solid black; padding: 5px;"> <p>This product contains Alfalfa (<i>Medico sativa</i>). Individual with a predisposition to systemic lupus erythematosus should consult their physician before consuming this product.</p> </div>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
7.	<p><u>ALLOPURINOL</u></p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Allopurinol:</p> <p>WARNING</p> <p>Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction. Hypersensitivity to allopurinol usually appears after some weeks of therapy, and more rarely immediately after beginning treatment.</p> <p>In some instances, a skin rash may be followed by more severe reactions such as exfoliative, urticarial and purpuric lesion as well as Stevens-Johnson syndrome, and/or generalized vasculitis, irreversible hepatotoxicity and even death.</p>
8.	<p><u>ALPHA DIHYDROERGOCRYPTINE</u></p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>
9.	<p><u>ALPRAZOLAM</u></p> <p>Please refer to SEDATIVE – HYPNOTIC PRODUCTS</p>
10.	<p><u>AMIODARONE</u></p> <p>The following <u>boxed warning</u> shall be <u>included on the package inserts</u> of products containing Amiodarone:</p> <div data-bbox="316 1480 1386 1632" style="border: 1px solid black; padding: 10px; margin: 10px 0;"> <p>This product is to be used only by a registered medical practitioner with experience in cardiology.</p> </div>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
11.	<p><u>ANTIDEPRESSANTS</u></p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products used as antidepressants:</p> <p>WARNING</p> <p><u>Suicidality in Children and Adolescents</u></p> <ul style="list-style-type: none"> • Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. • Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need. • Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. • Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber. • The indication(s) approved in paediatric for the particular drug should be clearly stated / included. <p><i>Reference: Circular Bil(41)dIm BPFK/02/5/1.3: Keputusan Pihak Berkuasa Kawalan Dadah (PBKD) Berhubung Tambahan Amaran Berkaitan Dengan 'Suicidality In Children And Adolescents Treated With Antidepressants'</i></p>
12.	<p><u>ANTIEPILEPTICS</u></p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products used as antiepileptics:</p> <p>WARNING AND PRECAUTION</p> <p>Potential for an increase in risk of suicidal thoughts or behaviors.</p> <p><i>Reference: Circular Bil (43) dIm. BPFK/PPP/01/03: Kenyataan Amaran Berkaitan Dengan "Potential for an Increase in Risk of Suicidal Thoughts or Behaviours" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Antiepileptik</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
13.	<p data-bbox="276 297 687 338"><u>ANTIPSYCHOTIC AGENTS</u></p> <p data-bbox="276 371 831 412"><u>13.1 ALL ANTIPSYCHOTIC AGENTS</u></p> <p data-bbox="347 434 1409 510">The following statement shall be <u>included in the package inserts</u> of products containing antipsychotic:</p> <p data-bbox="347 544 831 584">PREGNANCY AND LACTATION</p> <p data-bbox="347 607 1409 862">Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.</p> <p data-bbox="347 884 1409 960">[BRAND NAME] should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.</p> <p data-bbox="347 987 1409 1115"><i>Reference: Circular Bil (16) dlm BPFK/PPP/01/03 Jld 1: Direktif Kenyataan Amaran Berkaitan Dengan Risiko Extrapyramidal And/or Withdrawal Symptoms Bagi Neonat Yang Terdedah Kepada Produk Antipsikotik Semasa Trimester Ketiga Kehamilan Pada Sisip Bungkusan Semua Produk Antipsikotik</i></p> <p data-bbox="276 1182 930 1223"><u>13.2 ATYPICAL ANTIPSYCHOTIC AGENTS</u></p> <p data-bbox="347 1245 1409 1321">The following statement shall be <u>included in the package inserts</u> of products containing atypical antipsychotic agents:</p> <ol data-bbox="347 1321 584 1576" style="list-style-type: none"> Clozapine Olanzapine Risperidone Quetiapine Ziprasidone Aripiprazole <p data-bbox="347 1632 509 1673">WARNING</p> <p data-bbox="347 1706 882 1747"><u>Hyperglycemia and Diabetes Mellitus</u></p> <p data-bbox="347 1769 1409 2024">Hyperglycemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given this confounders, the</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p>relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.</p> <p>Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.</p> <p><i>Reference: Circular Bil (31)dIm BPFK/02/5/1.3: Tambahan Amaran Berkaitan Dengan Hyperglycemia Bagi Keluaran 'Atypical Antipsychotic Agents'</i></p>
14.	<p>APOMORPHINE</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>
15.	<p>ARGININE</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of oral preparations containing Arginine for health supplement products:</p> <p>WARNING</p> <p>Arginine is not recommended for patients following a heart attack.</p> <p><i>Reference: Circular Bil (64) dIm BPFK/02/5/1.3: Pernyataan Amaran Produk Mengandung 'Arginine'</i></p>
16.	<p>ARIPIRAZOLE</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
17.	<p>ASPARTAME</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of products containing Aspartame:</p> <p>WARNING</p> <p>Unsuitable for phenylketonurics.</p>
18.	<p>BEE POLLEN</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of product containing bee pollen:</p> <p style="padding-left: 40px;">This product contains Bee Pollen and may cause severe allergic reactions, including fatal anaphylactic reactions in susceptible individuals.</p> <p style="padding-left: 40px;">Asthma and allergy sufferers may be at greater risks.</p>
19.	<p>BENZOYL PEROXIDE</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of products containing Benzoyl peroxide:</p> <p>WARNING</p> <p>Do not use this medication if you have sensitive skin or if you are sensitive to benzoyl peroxide. This product may cause irritation, characterized by redness, burning, itching, peeling, or possible swelling.</p>
20.	<p>BENZYL ALCOHOL</p> <p>The following <u>statement</u> shall be <u>included on label and in package insert</u> of parenteral products containing Benzyl alcohol:</p> <div style="border: 1px solid black; padding: 10px; margin-top: 10px;"> <p>As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age.</p> <p>Not to be used in neonates.</p> </div>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
21.	<p>BLACK COHOSH (<i>CIMICIFUGAE RACEMOSAE</i>)</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of products containing Black Cohosh (<i>Cimicifugae Racemosae</i>):</p> <p>WARNING</p> <p>Stop taking this product if signs and symptoms suggestive of liver injury develop such as tiredness, loss of appetite, yellowing of the skin and eyes or severe upper stomach pain with nausea and vomiting or dark urine and consult your doctor immediately.</p> <p>Patients using herbal medicinal products should tell their doctor about it.</p> <p><i>Reference: Circular Bil (61) dlm BPFK/02/5/1.3: Pernyataan Amaran Produk Mengandungi 'Black Cohosh'</i></p>
22.	<p>BROMAZEPAM</p> <p>Please refer to SEDATIVE – HYPNOTIC PRODUCTS</p>
23.	<p>BROMOCRIPTINE</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>
24.	<p>BROMPHENIRAMINE</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of liquid oral products containing Brompheniramine:</p> <p>WARNING</p> <p>When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
25.	<p>CAMPHOR</p> <p>25.1 The following <u>boxed warning</u> shall be <u>included on the labels</u> of products containing Camphor:</p> <div data-bbox="323 479 1385 725" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>CAN CAUSE CONVULSION</p> <p>CONTRAINDICATED IN CHILDREN BELOW 2 YEARS OF AGE. CAUTION MUST BE EXERCISED WHEN OLDER CHILDREN ARE TREATED</p> <p>AVOID DIRECT APPLICATION INTO THE NOSTRILS</p> </div> <p>25.2 The following <u>warning and precaution</u> shall be <u>included in the package insert</u> of products containing Camphor:</p> <p>WARNING</p> <p>This product is contraindicated in children below 2 years of age. Caution must be exercised when older children are treated.</p> <p>PRECAUTION:</p> <p>It is dangerous to place any camphor containing product into the nostril of children. A small amount applied this way may cause immediate collapse.</p>
26.	<p>CARBAMAZEPINE</p> <p>The following <u>statement</u> shall be <u>included in the package insert</u> of products containing Carbamazepine:</p> <p>Severe dermatologic reactions including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's Syndrome) have been reported with carbamazepine. Patients treated with carbamazepine should closely be monitored for signs of hypersensitivity reactions, particularly during the first month of therapy. Immediate discontinuation of therapy should be made when cutaneous reactions occur.</p> <p>Potential for an increase in risk of suicidal thoughts or behaviours.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
27.	<p>CARBIMAZOLE</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Carbimazole:</p> <p>WARNING</p> <p>Carbimazole may cause white cell disorders such as neutropenia and agranulocytosis, which may be fatal if treatment with carbimazole is not stopped promptly. These reactions usually occur during the first 3 months of therapy, and in most cases, are reversible on stopping treatment. Since agranulocytosis can develop very rapidly, periodic leucocyte counts alone may not be effective in the early detection of these reactions.</p>
28.	<p>CABERGOLINE</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>
29.	<p>CEFTRIAZONE</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Ceftriazone:</p> <p>CONTRAINDICATION</p> <p>Ceftriazone is contraindicated in neonates (≤ 28 days of age) if they require (or are expected to require) treatment with calcium-containing intravenous solutions, including calcium-containing infusions such as parenteral nutrition, because of the risk of precipitation of ceftriazone-calcium.</p> <p>WARNING</p> <ul style="list-style-type: none"> • In patients other than neonates, Ceftriazone and calcium-containing solutions may be administered sequentially to one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid. • Diluents containing calcium, such as Ringer's solution or Hartmann's solution, are not to be used to reconstitute Ceftriazone vials or to further dilute a reconstituted vial for intravenous administration because a precipitate can form. Ceftriazone must not be administered simultaneously with calcium-containing intravenous solutions, including continuous calcium-containing infusions such as parenteral nutrition via a Y-site, because precipitation of ceftriazone-calcium can occur. <p>Reference: <i>Circular Bil (48) dlm. BPFK/PPP/01/03: Pindaan Pada Kenyataan Amaran Berkaitan Dengan "Potential Risk Associated With Concomitant Use Of Ceftriazone With Calcium - Containing Intravenous Solutions" Yang Perlu Dimuatkan Pada Sisip Bungkus Produk Ceftriazone</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
30.	<p>CETIRIZINE</p> <p>The following <u>statement</u> shall be <u>included in the package insert</u> of products containing Cetirizine:</p> <p>PRECAUTION</p> <p>Activities Requiring Mental Alertness: In clinical trials the occurrence of somnolence has been reported in some patients taking Cetirizine: due caution should therefore be exercised when driving a car or operating potentially dangerous machinery.</p>
31.	<p>CHELIDONIUM MAJUS</p> <p>The following <u>statement</u> shall be <u>included on the label</u> of products containing <i>Chelidonium majus</i> in 2 languages (<i>Bahasa Melayu</i> and English) in bold font:</p> <p>WARNING</p> <p>This product may cause adverse reaction to the liver.</p> <p>AMARAN</p> <p><i>Produk ini mungkin boleh menyebabkan kesan sampingan pada hepar (hati).</i></p> <p>Reference: Circular (bil 17) dlm bpfk02/5/1.3: Label Amaran Tentang Penggunaan Bahan Chelidonium majus</p>
32.	<p>CHITOSAN</p> <p>The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of products containing chitosan.</p> <p>“DERIVED FROM SEAFOOD”</p> <p>Reference: Circular Bil (52) dlm BPFK/02/5/1.3: Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Dari Sumber Laut'</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
33.	<p>CHLORPHENIRAMINE</p> <p>The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of liquid oral products containing Chlorpheniramine:</p> <p>WARNING</p> <p>When used for treatment of cough and cold;</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>
34.	<p>CHORIONIC GONADOTROPHIN</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Chorionic gonadotrophin:</p> <p>The ovulation cycle should be monitored with oestriol levels and ultrasonography</p>
35.	<p>CLEMASTINE</p> <p>The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of liquid oral products containing Clemastine:</p> <p>WARNING</p> <p>When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
36.	<p>CLINDAMYCIN</p> <p>The package insert must emphasize the possibility of pseudomembranous colitis with the use of the drug.</p> <p>The <u>package insert</u> must <u>include</u> the <u>following boxed or emphasized statements/ warning:</u></p> <ul style="list-style-type: none"> • Clindamycin therapy has been associated with severe colitis which may end fatally. • It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. • It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. • Its use in newborns is contraindicated.
37.	<p>CLOBAZAM</p> <p>Please refer to SEDATIVE – HYPNOTIC PRODUCTS</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
38.	<p>CLOPIDOGREL</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Clopidogrel:</p> <p>SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE Pharmacogenetics: Based on literature data, patients with genetically reduced CYP2C19 function (intermediate or poor metabolisers) have lower systemic exposure to the active metabolite of clopidogrel and diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than do patients with normal CYP2C19 function.</p> <p>INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION Since clopidogrel is metabolised to its active metabolite by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel and a reduction in clinical efficacy. Concomitant use of drugs that inhibit CYP2C19 (e.g proton pump inhibitors) should be discouraged.</p> <p>PHARMACOKINETIC PROPERTIES The oxidative step is regulated primarily by Cytochrome P450 ISOENZYMES 2B6, 3A4, 1A1, 1A2 and 2C19.</p> <p><i>Reference: Circular Bil (42) dlm. BPFK/PPP/01/03: Kenyataan Amaran Berkaitan Dengan "Possible Interaction Between Clopidogrel and Proton Pump Inhibitors" yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Clopidogrel</i></p>
39.	<p>CLOZAPINE</p> <p>Please refer to ANTIPSYCHOTIC AGENT</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
40.	<p data-bbox="276 297 480 331">COLCHICINE</p> <p data-bbox="276 371 1409 445">The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Colchicines:</p> <p data-bbox="276 483 1409 557">INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:</p> <p data-bbox="276 602 1409 808">Potential risk of severe drug interactions, including death, in certain patients treated with colchicine and concomitant P-glycoprotein or strong CYP3A4 inhibitors such as clarithromycin, cyclosporin, erythromycin, calcium channel antagonists (e.g Verapamil and Diltiazem), telithromycin, ketoconazole, itraconazole, HIV protease inhibitors and nefazodone.</p> <p data-bbox="276 860 1409 934">P-Glycoprotein or strong CYP3A4 inhibitors are not to be used in patients with renal or hepatic impairment who are taking colchicine.</p> <p data-bbox="276 985 1409 1153">A dose reduction or interruption of colchicine treatment should be considered in patients with normal renal and hepatic function if treatment with a P-glycoprotein or a strong CYP3A4 inhibitor is required. Avoid consuming grapefruit and grapefruit juice while using colchicine.</p> <p data-bbox="276 1189 1409 1283">Reference: <i>Circular Bil (45) dlm. BPFK/PPP/01/03: Kenyataan Amaran Berkaitan Dengan "Severe Drug Interaction Between Colchicine and P-Glycoprotein or Strong CYP3A4 Inhibitors" Yang Perlu Dimuatkan Pada Sisip Bungkusan Produk Colchicine</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
41.	<p>COX-2 INHIBITORS</p> <p>The following <u>statement</u> shall be <u>included in the package insert</u> for COX-2 Inhibitors products containing Celecoxib and Etoricoxib:</p> <ul style="list-style-type: none"> • Contraindication for patients who have increased risk of cardiovascular disease (ischemic heart disease and stroke). • Warning to prescriber when prescribing COX-2 Inhibitors to patients with risk factors of heart disease, hypertension (high blood pressure), hyperlipidemia, diabetes, smoking patient and patient with peripheral arterial disease. • Statement on limiting the period and dosing is written as 'Given the association between cardiovascular risk and exposure to COX-2 Inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment'. • Contraindication for patient using Etoricoxib is written as 'Contraindication for Etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control'. <p><i>Reference: Circular Bil (46) dlm BPFK/02/5/1.3: Keputusan Mesyuarat PBKD - Tindakan-tindakan regulatori terhadap Cox-2 Inhibitors: Celecocib dan Etoricoxib</i></p>
42.	<p>CYPROTERONE ACETATE</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Cyproterone acetate:</p> <p>WARNING</p> <p>Direct hepatic toxicity, including jaundice, hepatitis and hepatic failure, which has been fatal in some cases, has been reported in patients treated with 100mg or more of cyproterone acetate. Most reported cases are in men with prostatic cancer. Toxicity is dose-related and develops, usually, several months after treatment has begun. Liver function tests should be performed pre-treatment and whenever any symptoms or signs suggestive of hepatotoxicity occur. If hepatotoxicity is confirmed, cyproterone acetate should normally be withdrawn, unless the hepatotoxicity can be explained by another cause, e.g. metastatic disease, in which case cyproterone acetate should be continued only if the perceived benefit outweighs the risk.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
43.	<p>CYTOTOXIC AGENT</p> <p>The following <u>boxed statement</u> shall be <u>included on the label</u> of products containing Cytotoxic agents:</p> <div data-bbox="331 474 1380 551" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>CAUTION : CYTOTOXIC AGENT</p> </div> <p>Note: The label caution should be printed prominently on the label.</p>
44.	<p>DEXBROMPHENIRAMINE</p> <p>The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of liquid oral products containing Dexbrompheniramine:</p> <p>WARNING When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p>Reference: <i>Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>
45.	<p>DEXTROMETHORPHAN</p> <p>The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of liquid oral products containing Dextromethorphan:</p> <p>WARNING When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p>Reference: <i>Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
46.	<p>DIAZEPAM</p> <p>Please refer to SEDATIVE – HYPNOTIC PRODUCTS</p>
47.	<p>DICLOFENAC SODIUM</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Diclofenac sodium:</p> <p>PRECAUTION</p> <p>Severe cutaneous reactions, including Stevens - Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), have been reported with diclofenac sodium. Patients treated with diclofenac sodium should be closely monitored for signs of hypersensitivity reactions. Discontinue diclofenac sodium immediately if rash occurs.</p> <p>Adverse effects: Dermatological: Occasional - rashes or skin eruptions Cases of hair loss, bullous eruptions, erythema multiforme, Stevens- Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), and photosensitivity reactions have been reported.</p>
48.	<p>DICYCLOMINE</p> <p>The following <u>boxed warning</u> shall be <u>included on the labels and in the package inserts</u> of products containing Dicyclomine:</p> <div data-bbox="323 1395 1374 1581" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>WARNING</p> <p>Dicyclomine is not recommended for use in infants under the age of six month</p> </div>

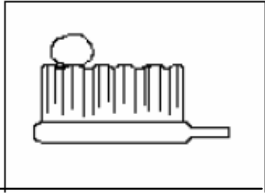
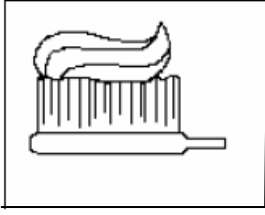
NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
49.	<p>DIPHENHYDRAMINE</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of products containing Diphenhydramine:</p> <p>WARNING</p> <p>When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p>Reference: <i>Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
50.	<p data-bbox="276 297 555 331">DIPHENOXYLATE</p> <p data-bbox="276 365 1409 443">50.1 The following <u>boxed warning</u> shall be <u>included on the labels</u> of products containing Diphenoxylate:</p> <div data-bbox="328 488 1390 577" style="border: 1px solid black; padding: 5px; text-align: center;"> <p data-bbox="355 510 1362 544">NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE.</p> </div> <p data-bbox="276 611 1409 689">50.2 The following <u>statement</u> shall be <u>included in the package insert</u> of products containing Diphenoxylate:</p> <p data-bbox="355 701 520 734">WARNING</p> <div data-bbox="328 745 1390 835" style="border: 1px solid black; padding: 5px; text-align: center;"> <p data-bbox="456 779 1262 813">Not recommended for children under 6 years of age.</p> </div> <p data-bbox="355 880 576 913">PRECAUTION</p> <p data-bbox="355 947 1409 1361">Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid detention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes, especially in young children. If severe dehydration of electrolyte imbalance is present, diphenoxylate should be withheld until appropriate corrective therapy has been initiated.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
51.	<p>DOPAMINERGIC INGREDIENT</p> <p>The following <u>warning/ statement related to “Sudden sleep onset”</u> shall be included in the package insert and product literature of products containing dopaminergic ingredients:</p> <ol style="list-style-type: none"> alpha-dihydroergocryptine apomorphine bromocriptine cabergoline levodopa lisuride piribedil pramipexole quinagolide ropinirole <p>SPECIAL WARNING & SPECIAL PRECAUTIONS FOR USE</p> <p>..... has been associated with somnolence and episodes of sudden onset, particularly in patients with Parkinson’s diseases. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported very rarely. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered.</p> <p>EFFECTS ON ABILITY TO DRIVE AND USE MACHINES</p> <p>Patients being treated with and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also section on special warnings and special precautions for use).</p> <p>UNDESIRABLE EFFECTS</p> <p>..... is associated with somnolence and has been associated very rarely with excessive daytime somnolence and <u>sudden sleep onset</u> episodes.</p> <p>Reference: <i>Circular (bil 14) dlm bpfk02/5/1.3: keluaran yang mengandung bahan aktif dopaminergik- tanda amaran berkaitan dengan ' sudden sleep onset'</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
52.	<p>EPHEDRINE</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of products containing Ephedrine:</p> <p>WARNING</p> <p>When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>
53.	<p>FAMOTIDINE</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Famotidine:</p> <p>DOSAGE</p> <p>Dosage adjustment is required for patients with moderate to severe renal insufficiency. Since CNS adverse effects have been reported in patients with moderate to severe renal insufficiency, to avoid excess accumulation of the drug, the dose of famotidine may be reduced to half the recommended dose or the dosing interval may be prolonged to 36 - 48 hours as indicated by the patient's clinical response.</p> <p>PRECAUTION</p> <p>As elderly patients are more likely to have decreased clearance of famotidine, care should be taken in dose selection and it may be useful to monitor renal function.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
54.	<p>FIBRATES</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Fibrates:</p> <ol style="list-style-type: none"> Clofibrate, Bezafibrate Ciprofibrate, Etofibrate Fenofibrate Simfibrate etc. <p>DRUG INTERACTION</p> <p>Concurrent use of fibates with HMG-CoA reductase inhibitors may cause severe myositis and myoglobinuria.</p>
55.	<p>FLUCLOXACILLIN</p> <p>The following <u>warning</u> shall be <u>included in the package insert</u> of products containing Flucloxacillin:</p> <div data-bbox="317 1135 1382 1473" style="border: 1px solid black; padding: 10px; margin: 10px 0;"> <p style="text-align: center;">WARNING</p> <p style="text-align: center;">Liver Toxicity</p> <p>Flucloxacillin can cause severe hepatitis and cholestatic jaundice, which may be protracted. This reaction is more frequent in older patients and those who take the drug for prolonged periods (see Precaution, Adverse Reactions)</p> </div>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
56.	<p data-bbox="276 297 448 331">FLUORIDE</p> <p data-bbox="276 371 1406 443">All toothpastes containing Fluorides should be labeled with the following additional information:</p> <p data-bbox="325 472 699 506">a. DIRECTIONS ON USE</p> <ul data-bbox="373 517 1011 551" style="list-style-type: none"> • Do not swallow – spit and rinse after use. <p data-bbox="325 595 884 629">b. FOR CHILDREN BELOW 6 YEARS</p> <ul data-bbox="373 640 1219 719" style="list-style-type: none"> • Use a pea-sized amount of toothpaste (less than 5mm). • Supervise child's brushing. <p data-bbox="325 763 900 797">c. DIRECTIONS ON DENTAL HEALTH</p> <ul data-bbox="373 808 1139 931" style="list-style-type: none"> • Brush at least twice a day. • Restrict the amount and frequency of sugary food. • Visit your dentist at least once a year. <p data-bbox="325 976 724 1010">d. GRAPHICS AS SHOWN</p> <ul data-bbox="373 1021 572 1099" style="list-style-type: none"> • <i>Child's use</i> • <i>Adult's use</i> <div data-bbox="517 1155 783 1346">  <p data-bbox="975 1245 1126 1279"><i>Child's use</i></p> </div> <div data-bbox="517 1413 783 1626">  <p data-bbox="975 1491 1126 1525"><i>Adult's use</i></p> </div>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
57.	<p>FLUOROQUINOLONES</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing fluoroquinolones:</p> <p>WARNING AND PRECAUTION</p> <p><u>Exacerbation of myasthenia gravis</u> Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis</p> <p>ADVERSE REACTIONS/SIDE EFFECTS</p> <p><u>Exacerbation of myasthenia gravis</u> Post Marketing Experience</p> <p><i>Reference: Circular Bil (20) dlm BPFK/PPP/01/03 Jld 1: Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Exacerbation of Myasthenia Gravis dalam Sisip Bungkusan Semua Produk Antibiotik dalam Kumpulan Fluoroquinolones</i></p>
58.	<p>FLURAZEPAM HYDROCHLORIDE</p> <p>Please refer to SEDATIVE – HYPNOTIC PRODUCTS</p>
59.	<p>GADOBENIC ACID</p> <p>Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING</p>
60.	<p>GADOBUTROL</p> <p>Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
61.	GADODIAMIDE Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
62.	GADOLINIUM OXIDE Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
63.	GADOTERIC ACID Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
64.	GADOVERSETAMIDE Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
65.	GADOXETIC ACID Please refer to GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING
66.	GADOLINIUM BASED CONTRAST MEDIUM FOR MAGNETIC RESONANCE IMAGING The following <u>boxed warning and warning</u> shall be <u>included in the package inserts</u> of products containing: <ul style="list-style-type: none"> a. Gadobenate Dimeglumine b. Gadobenic acid c. Gadobutrol d. Gadodiamide e. Gadolinium oxide f. Gadoteric acid g. Gadoversetamide h. Gadoxetic acid

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p>BOXED WARNING</p> <div data-bbox="296 360 1399 1249" style="border: 1px solid black; padding: 10px;"> <ul style="list-style-type: none"> - Exposure to gadolinium – based contrast agents (GBCAs) increases the risk for Nephrogenic Systemic Fibrosis (NSF) in patients with: <ul style="list-style-type: none"> • acute or chronic severe renal insufficiency (glomerular filtration rate < 30mL/min/1.73m²), or • acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period. - NSF is a debilitating and sometimes fatal disease affecting the skin, muscle, and internal organs - Avoid use of GBCAs unless the diagnostic information is essential and not available with non-contrast enhanced magnetic resonance imaging (MRI). - Screen all patients for renal dysfunction by obtaining a history and/ or laboratory tests. - When administering a GBCA, do not exceed the dose recommended in product labelling. Allow sufficient time for elimination of the GBCA prior to any readministration. </div> <p>WARNING</p> <ul style="list-style-type: none"> • Among the factors that may increase the risk for NSF are repeated or higher than recommended doses of a GBCA. • For patients receiving haemodialysis, healthcare professionals may consider prompt haemodialysis following GBCA administration in order to enhance the contrast agent's elimination. However, it is unknown if haemodialysis prevents NSF. • Determine the renal function of patients by obtaining a medical history of conducting laboratory tests that measure renal function prior to using GBCA. • The risk, if any, for developing NSF among patients with mild to moderate renal insufficiency or normal renal function is unknown. • Post-marketing reports have identified the development of NSF following single and multiple administrations of GBCAs.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p>Reference: Circular Bil (2) dlm. BPFK/PPP/01/03 Jld. 1: PENAMBAHAN AMARAN BERKOTAK DAN AMARAN TERKINI KE DALAM SISIP BUNGKUSAN SEMUA AGEN "CONTRAST MEDIUM" YANG BERASASKAN GADOLINIUM (GADOLINIUM BASED) UNTUK TUJUAN 'MAGNETIC RESONANCE IMAGING' "</p>
67.	<p>GENTAMICIN TOPICAL PREPARATIONS</p> <p>The following <u>boxed statement</u> shall be <u>included in the package inserts</u> of topical Gentamicin preparations:</p> <div data-bbox="319 678 1393 790" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>Use of topical gentamicin preparations in closed hospital settings is actively discouraged</p> </div>
68.	<p>GINKGO BILOBA/ GINKGO EXTRACT</p> <p>The following <u>statements</u> shall be <u>included on the labels and in the package inserts</u> of products containing <i>Ginkgo biloba</i>/ Ginkgo extract:</p> <p>As the use of Ginkgo may increase the tendency of bleeding, please consult your physician/ pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/dental procedure.</p> <p><i>(Memandangkan Ginkgo boleh meningkatkan kemungkinan pendarahan, sila rujuk kepada doktor/ ahli farmasi sekiranya anda sedang atau akan menggunakan ubat lain dan sebelum prosedur pembedahan / dental dijalankan).</i></p> <p>Reference: Circular Bil (47) dlm BPFK/02/5/1.3: Pernyataan Amaran Pada Label Dan Sisip Bungkus Produk Yang Mengandungi Ginkgo Biloba / Ginkgo Ekstrak</p>
69.	<p>GINSENG</p> <p>The following <u>statements</u> shall be <u>included on the labels and in the package inserts</u> of products containing Ginseng (including all Panax genus):</p> <ul style="list-style-type: none"> • Contraindicated in pregnant women. • Safe use in lactating women and children has not been established. • Do not exceed the stated dose. • Safety on long term use has not been established.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
70.	<p>GLUCOSAMINE</p> <p>70.1 The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of products containing Glucosamine (derived from seafood);</p> <p style="text-align: center;">“DERIVED FROM SEAFOOD”</p> <p>70.2 The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Glucosamine:</p> <p>SIDE EFFECT</p> <ul style="list-style-type: none"> • Cardiovascular Peripheral oedema, tachycardia were reported in a few patients following larger clinical trials investigating oral administration in osteoarthritis. Causal relationship has not been established. • Central nervous system Drowsiness, headache, insomnia have been observed rarely during therapy (less than 1%). • Gastrointestinal Nausea, vomiting, diarrhoea, dyspepsia or epigastric pain, constipation, heartburn and anorexia have been described rarely during oral therapy with glucosamine. • Skin Skin reactions such as erythema and pruritus have been reported with therapeutic administration of glucosamine. <p>Reference:</p> <ol style="list-style-type: none"> a) Circular Bil (52) dlm BPFK/02/5/1.3: Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan AKtif Adalah Dari Sumber Laut' b) Circular Bil (72) dlm BPFK/02/5/1.3: Mengemaskini dan menyelaraskan maklumat mengenai kesan sampingan pada label & sisip bungkusan produk yang mengandungi glucosamine
71.	<p>HIV PROTEASE INHIBITORS</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing HIV Protease inhibitors:</p> <p>ADVERSE REACTION</p> <p>Although a causal relationship has not been definitively established, protease inhibitors may contribute to increase in blood sugar levels and even diabetes in HIV patients. Close monitoring of blood glucose level is recommended.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
72.	<p>HYDROQUINONE</p> <p>The following <u>warning</u> shall be <u>included on the outer labels</u> of products containing Hydroquinone:</p> <p>WARNING: Some users of this product may experience skin irritations. Should this occur, stop using and consult a medical doctor.</p> <p>For hydroquinone products that do not contain any sun screening agent, a statement should be included in the package insert to advise users to either use a sun screening agent or protect themselves from sunlight or to use the products only at night.</p> <p><i>Reference: Circular (bil 26) dlm bpfkweb.bpkp.3.2000: Amaran bagi Produk Mengandung Hydroquinone</i></p>
73.	<p>IMMUNOSUPPRESANTS</p> <p>The following <u>information</u> shall be <u>included in the package inserts</u> of products containing the following immunosuppressants:</p> <ul style="list-style-type: none"> a) Sirolimus b) Cyclosporin c) Mycophenolate mofetil d) Mycophenolic acid e) Tacrolimus <p>WARNINGS AND PRECAUTIONS</p> <p>Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus associated nephropathy which has been observed in patients receiving immunosuppressants. These infections may lead to serious, including fatal outcomes.</p> <p><i>Reference: Circular Bil (44) dlm. BPFK/PPP/01/03: Kenyataan Amaran Berkaitan Dengan "Increased Risk For Opportunistic Infections Such As Activation of Latent Viral Infections Including BK Virus – Associated Nephropathy" Yang Perlu Dimuatkan Pada Sisip Bungkus Produk Immunosuppressant</i></p>
74.	<p>INSULIN</p> <p>The label of the product shall <u>state clearly the source</u> of insulin.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
75.	<p>INGREDIENTS DERIVED FROM SEAFOOD</p> <p>The following <u>statement</u> shall be <u>included on the labels and package inserts</u> of products.</p> <p style="text-align: center;">“DERIVED FROM SEAFOOD”</p> <p><i>Reference: Circular Bil (52) dlm BPFK/02/5/1.3: Muatkan Kenyataan 'Derived From Seafood' Pada Label Produk Jika Bahan Aktif Adalah Dari Sumber Laut'</i></p>
76.	<p>KAOLIN, PECTIN, KAOLIN-PECTIN</p> <p>The following <u>boxed warning</u> shall be <u>included on the labels</u>:</p> <div data-bbox="300 860 1401 954" style="border: 1px solid black; padding: 5px; text-align: center;"> <p>NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE.</p> </div> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing kaolin and/ or pectin:</p> <p>WARNING</p> <div data-bbox="300 1214 1401 1303" style="border: 1px solid black; padding: 5px; text-align: center;"> <p>Not recommended for children under 6 years of age.</p> </div> <p>Severe constipation, which may lead to faecal impaction, may rarely occur in children and the elderly patients taking kaolin and pectin. Kaolin and pectin may interfere with the absorption of other drugs, including antibiotics, administered concurrently.</p> <p>PRECAUTION</p> <p>Appropriate fluid and electrolyte therapy should be given to protect against dehydration. Oral rehydration therapy with the use of appropriate fluids including oral rehydration salts - remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
77.	<p data-bbox="277 300 550 336">KETOCONAZOLE</p> <p data-bbox="277 371 1407 448">The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing ketoconazole:</p> <p data-bbox="277 483 628 519">CONTRAINDICATIONS</p> <p data-bbox="277 546 928 582">In patients with acute or chronic liver disease.</p> <p data-bbox="277 618 734 654">WARNINGS & PRECAUTIONS</p> <div data-bbox="287 689 1391 1084" style="border: 1px solid black; padding: 10px;"> <p data-bbox="296 716 1382 869">Because of the risk for serious hepatotoxicity, [BRAND NAME] should be used only when the potential benefits are considered to outweigh the potential risks, taking into consideration the availability of other effective antifungal therapy.</p> <p data-bbox="296 904 1382 1012">Assess liver function, prior to treatment to rule out acute or chronic liver disease, and monitor at frequent and regular intervals during treatment, and at the first signs or symptoms of possible hepatotoxicity.</p> </div> <p data-bbox="277 1106 504 1142"><u>Hepatotoxicity</u></p> <p data-bbox="277 1146 1407 1326">Very rare cases of serious hepatotoxicity, including cases with a fatal outcome or requiring liver transplantation have occurred with the use of oral ketoconazole. Some patients had no obvious risk factors for liver disease. Cases have been reported that occurred within the first month of treatment, including some within the first week.</p> <p data-bbox="277 1352 1407 1684">The cumulative dose of the treatment is a risk factor for serious hepatotoxicity. Factors which may increase the risk of hepatitis are prolonged treatment with ketoconazole tablets, females over 50 years of age, previous treatment with griseofulvin, a history of liver disease, known drug intolerance and concurrent use of medication which compromises liver function. A period of one month should be allowed between cessation of griseofulvin treatment and commencement treatment with ketoconazole tablets because of an apparent association between recent griseofulvin therapy and hepatic reactions to ketoconazole tablets.</p> <p data-bbox="277 1711 1407 1792">Monitor liver function in all patients receiving treatment with ketoconazole tablets (see Monitoring of hepatic function).</p> <p data-bbox="277 1818 1407 1962">Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, jaundice, abdominal pain or dark urine. In these patients, treatment should be stopped immediately and liver function should be conducted.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p><u>Monitoring of hepatic function</u></p> <p>Monitor liver function in all patients receiving treatment with ketoconazole tablets. Monitor liver function prior to treatment to rule out acute or chronic liver disease (see CONTRAINDICATIONS), after two weeks of treatment and then on a monthly basis and at the first signs or symptoms of possible hepatic toxicity. When the liver function tests indicate liver injury, the treatment should be stopped immediately.</p> <p>A risk and benefit evaluation should be made before oral ketoconazole is used in cases of non-life threatening diseases requiring long treatment periods.</p> <p>In patients with elevated liver enzymes, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases, close monitoring of the liver enzymes is necessary.</p> <p>UNDESIRABLE EFFECTS</p> <p><u>Post-marketing Experience</u></p> <p><i>Hepato-biliary Disorders</i></p> <p>Very rare: serious hepatotoxicity, including hepatitis cholestatic, biopsy-confirmed hepatic necrosis, cirrhosis, hepatic failure including cases resulting in transplantation or death (see WARNINGS & PRECAUTIONS).</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
78.	<p>KETOROLAC TROMETHAMOL (KETOROLAC TROMETHAMINE)</p> <p>The following <u>statements</u> shall be <u>included in the package inserts</u> of products containing Ketorolac tromethamol:</p> <p>THE PRODUCT SHALL BE INDICATED FOR THE FOLLOWING For short-term management of moderate to severe acute post-operative pain following surgical procedures associated with low risk of haemorrhage.</p> <p>DOSAGE AND DURATION OF TREATMENT Parenteral administration: The starting dose should be 10mg with subsequent doses of 10-30mg four to six hourly as required. The lowest effective dose should be used. The total daily dose of 90mg for the non-elderly and 60mg for the elderly should not be exceeded. Maximum duration of parenteral treatment is 2 days for all age groups. In patients who have received parenteral ketorolac and are converted to oral tablets, the total combined daily dose of all forms of ketorolac should not exceed 90mg for non-elderly and 60mg for the elderly. Maximum duration of treatment for the oral formulation is 7 days.</p> <p>CONTRAINDICATIONS</p> <ul style="list-style-type: none"> • A history of peptic ulceration or gastrointestinal bleeding • A history of haemorrhagic diathesis • A history of confirmed or suspected cerebrovascular bleeding • Operations associated with a high risk of haemorrhage • A history of asthma • Moderate or severe renal impairment (serum creatinine > 160 μmol/L) • Hypovolaemia or dehydration from any cause • Hypersensitivity to NSAIDs or aspirin • During pregnancy, labour, delivery or lactation • Concomitant administration with other NSAIDs, anticoagulant including low dose heparin
79.	<p>LEVODOPA</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
80.	<p>LINCOMYCIN</p> <p>For all products containing Lincomycin:</p> <p>The package insert must emphasize the possibility of pseudomembranous colitis with the use of the drug and must include the following boxed or emphasized statement/ warning:</p> <ol style="list-style-type: none"> Lincomycin therapy has been associated with severe colitis which may end fatally. It should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. It should not be used in patients with nonbacterial infections, such as most upper respiratory tract infections. Its use in newborns is contraindicated.
81.	<p>LISURIDE</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>
82.	<p>LIQUID PARAFFIN</p> <p>The following <u>statement</u> shall be <u>included on the labels</u> of products containing Liquid paraffin as laxative:</p> <ul style="list-style-type: none"> Not recommended for use in children below 3 years of age; Not recommended for use in pregnant women; Repeated use is not advisable; Consult your doctor if laxatives are needed every day, if you have persistent abdominal pain or have a condition which makes swallowing difficult.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
83.	<p data-bbox="276 297 496 331">LOPERAMIDE</p> <p data-bbox="276 365 1409 443">83.1 The following <u>boxed warning</u> shall be <u>included on the labels</u> of products containing Loperamide:</p> <div data-bbox="304 479 1402 562" style="border: 1px solid black; padding: 5px; text-align: center;"> <p data-bbox="355 506 1351 539">NOT RECOMMENDED FOR CHILDREN UNDER 6 YEARS OF AGE</p> </div> <p data-bbox="276 611 1409 689">83.2 The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Loperamide:</p> <p data-bbox="347 716 507 750">WARNING</p> <div data-bbox="304 772 1402 936" style="border: 1px solid black; padding: 5px;"> <p data-bbox="320 784 1386 891">Not recommended for children under 6 years of age. Its use has been associated with fatal episodes of paralytic ileus in infants and young children.</p> </div> <p data-bbox="347 974 563 1008">PRECAUTION</p> <p data-bbox="347 1041 1409 1406">Appropriate fluid and electrolyte therapy should be given to protect against dehydration in all cases of diarrhoea. Oral rehydration therapy which is the use of appropriate fluids including oral rehydration salts remains the most effective treatment for dehydration due to diarrhoea. The intake of as much of these fluids as possible is therefore imperative. Drug-induced inhibition of peristalsis may result in fluid retention in the intestine, which may aggravate and mask dehydration and depletion of electrolytes. If severe dehydration or electrolyte imbalance is present Loperamide should be withheld until appropriate corrective therapy has been initiated.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
84.	<p>LORATADINE</p> <p>The following <u>boxed warning</u> shall be <u>included in the package inserts</u> of products containing Loratadine:</p> <p>WARNING</p> <div data-bbox="288 551 1390 779" style="border: 1px solid black; padding: 10px;"> <p>Drugs known to inhibit hepatic metabolism should be co-administered with caution until definitive interaction studies can be completed. The number of subjects who concomitantly received macrolide antibiotics, ketoconazole, cimetidine, ranitidine, or theophylline along with loratadine in controlled clinical trials is too small to rule out possible drug interactions.</p> </div>
85.	<p>LORAZEPAM</p> <p>Please refer to SEDATIVE – HYPNOTIC PRODUCTS</p>
86.	<p>METHYL SALICYLATE</p> <p>The following <u>statements</u> shall be <u>included in the package inserts and product literature</u> of topical preparations containing methyl salicylate $\geq 5\%$:</p> <p>CAUTION</p> <p>This product contains methyl salicylate and when applied or rub on to the skin, can be absorbed through the skin into the blood. For patients taking warfarin, excessive application on to the skin for muscle or joint pains may increase the chances of bleeding.</p>
87.	<p>METHYLPHENIDATE HCL</p> <p>The following <u>boxed statement</u> shall be <u>included on the labels and in the package insert</u> of products containing Methylphenidate HCl:</p> <div data-bbox="325 1794 1390 1872" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>FOR SPECIALIST'S USE ONLY</p> </div>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
88.	<p>METOCLOPRAMIDE</p> <p>The following <u>statements</u> shall be <u>included in the package inserts</u> of products containing Metoclopramide:</p> <p>DOSAGE Total daily dose of metoclopramide, especially for children and young adults, should not normally exceed 0.5mg/kg body weight.</p> <p>WARNING</p> <ul style="list-style-type: none"> • Avoid doses exceeding 0.5mg/kg/day. • Extrapyramidal effects, especially dystonic reaction of metoclopramide are more likely to occur in children shortly after initiation of therapy, and usually with doses higher than 0.5mg per kg of body weight per day.
89.	<p>MICONAZOLE</p> <p>The following <u>boxed warning</u> shall be <u>included on the labels and in the package inserts</u> of intravaginal preparations containing Miconazole:</p> <div data-bbox="304 1133 1385 1505" style="border: 1px solid black; padding: 10px;"> <p>Sila dapatkan nasihat doktor atau ahli farmasi sebelum menggunakan keluaran ini jika anda mengambil ubat warfarin, iaitu sejenis ubat antipembekuan darah, kerana lebam/ pendarahan pada gusi/ hidung boleh berlaku secara spontan.</p> <p>(Please consult your physician/ pharmacist before using this product if you are on the anticoagulant medicine warfarin, because bleeding from nose/ gums or bruising may occur spontaneously).</p> </div> <p>Reference: Circular (bil 45) dlm bpfkweb.bpkp.2.2001: Keputusan Mesyuarat Pihak berkuasa Kawalan Dadah (PBKD) ke 122 Berhubung Amaran Berkaitan Interaksi Ubat Bagi Semua Keluaran ANTIFUNGAL INTRAVAGINAL Yang Mengandungi Miconazole</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
90.	<p>MIDAZOLAM</p> <p>The following <u>statements</u> shall be <u>included in the package inserts</u> of IV preparations containing Midazolam:</p> <p>WARNING</p> <p>IV Midazolam has been associated with severe respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy resulted. IV Midazolam should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory and cardiac functions. Assure immediate availability of resuscitative drugs, equipments, appropriate antidote and personnel trained in their use. Dosage of IV Midazolam must be individualized for each patient. Lower doses are usually required for elderly, debilitated or higher risk surgical patients. When Midazolam is administered intravenously for conscious sedation, it should be injected slowly (over at least 2 minutes); it should not be administered by rapid or single bolus IV injection because of respiratory depression and/or arrest, especially in elderly or debilitated patients. The initial dose may be as little as 1mg, but should not exceed 2.5mg in a normal healthy adult; administer over at least 2 minutes and allow additional 2 or more minutes to fully evaluate sedative effect. If further titration is necessary, use small increments to the appropriate level of sedation, allowing an additional 2 or more minutes after each increment to fully evaluate sedative effect. See Dosage and Administration for complete dosing information.</p> <p>Please refer to SEDATIVE – HYPNOTIC products for additional information.</p>
91.	<p>MINOXIDIL</p> <p>The label and the package insert shall include the following statement: To be supplied only on the prescription of a registered medical practitioner.</p> <p>Note: The statement is <u>exempted for external use preparation</u> containing not more than 5% of Minoxidil; its salts; its derivatives <i>(Please refer latest Poison List: Preparations for external use containing not more than 5% of Minoxidil; its salts; its derivatives, which is under Group C)</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
92.	<p>MUCOLYTIC AGENT</p> <p>The following <u>warning</u> shall be <u>included in the package inserts</u> of products containing:</p> <ol style="list-style-type: none"> Acetylcysteine Carbocysteine Methylcarbocysteine (Mecysteine) <p>CONTRAINDICATIONS</p> <p>Contraindicated in children below two (2) years of age.</p> <p><i>Reference: Circular Bil (7) dlm BPFK/PPP/01/03 Jld 1: Kemaskini Kenyataan Amaran "Contraindicated In Children Under 2 Years Of Age" Yang Wajib Dimuatkan Pada Sisip Bungkusan Semua Produk Carbocysteine, Acetylcysteine Dan Methylcarbocysteine (Mecysteine)</i></p>
93.	<p>NEVIRAPINE</p> <p>The following statement shall be included in the <u>package insert</u> of product that contains Nevirapine:</p> <p>Addition of this statement at approved Indication: "Avoid usage of Nevirapine in patient with CD4+cell count greater than 250cells/mm³".</p> <p><i>Reference: Circular Bil (43) dlm BPFK/02/5/1.3: Pendaftaran Produk Yang Mengandung Nevirapine</i></p>
94.	<p>NIFEDIPINE</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of "short acting" Nifedipine products:</p> <p>WARNING/ PRECAUTION</p> <p>Several well documented studies have described profound hypotension, myocardial infarction and death when immediate release nifedipine capsules are used sublingually for acute reduction of blood pressure.</p> <p>DOSAGE</p> <ul style="list-style-type: none"> Lower doses may be required in elderly patients as a result of reduced drug clearance. For hypertension, the dose used should not exceed 60mg daily.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
95.	<p>NITRATES</p> <p>The following <u>statements</u> shall be <u>included in the package inserts</u> of all “NITRATES FOR STABLE ANGINA PECTORIS”:</p> <ul style="list-style-type: none"> • An appropriate statement concerning the development of tolerance (under precaution section). A suggested statement would be as follows: ‘Development of tolerance may occur with all forms of nitrate therapy particularly with the long acting preparations that maintain continuously high plasma nitrate concentration’. • An appropriate recommendation on dosage regimens. The recommended dosage regimens should be one that is able to provide a low-nitrate period or a nitrate-free period of 8-12 hours every 24 hours to prevent the development of tolerance and thus maintain the antianginal effects.
96.	<p>NITRAZEPAM</p> <p>Please refer to SEDATIVE – HYPNOTIC PRODUCTS</p>
97.	<p>NORFLOXACIN</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Norfloxacin:</p> <p>PRECAUTION</p> <ol style="list-style-type: none"> Should not be used in children or pregnant women Phototoxicity may occur
98.	<p>NORMAL GLOBULIN</p> <p>INTRAMUSCULAR (IM)</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of Normal globulin IM preparations:</p> <p>WARNING</p> <p>Do not administer this preparation intravenously because of potential for serious hypersensitivity reactions.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
99.	<p data-bbox="276 297 472 331">NOSCAPINE</p> <p data-bbox="276 365 1409 443">99.1 The following <u>contraindication</u> shall be <u>included on the labels</u> of products containing Noscapine:</p> <div data-bbox="351 477 1382 566" style="border: 1px solid black; padding: 10px; text-align: center;"> <p data-bbox="459 499 1273 544">Contraindicated in Women of Child-bearing Potential</p> </div> <p data-bbox="276 611 1409 689">99.2 The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Noscapine:</p> <p data-bbox="347 723 507 757">WARNING</p> <p data-bbox="347 757 1409 981">Experimental data now suggests that noscapine may exhibit a mutagenic effect in vitro. Because of the possible consequent risk to the developing foetus, the products containing noscapine is contraindicated in women of child bearing potential, therefore pregnancy should be excluded before treatment, and effective contraception maintained throughout treatment with such products.</p> <p data-bbox="347 1014 563 1048">PRECAUTION</p> <p data-bbox="347 1048 1409 1160">In view of potential mutagenicity shown in vitro, potential risks should be balanced against anticipated benefits when treating children and neonates.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
100.	<p>NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID)</p> <p>The following <u>statement</u> shall be <u>included in the package insert</u> of products containing NSAID including COX-2 Inhibitors:</p> <p>WARNING</p> <p><u>Risk of GI Ulceration, Bleeding and Perforation with NSAID</u> Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.</p> <p>Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.</p>
101.	<p>OLANZAPINE</p> <p>Please refer to ANTIPSYCHOTIC AGENT</p>
102.	<p>PARACETAMOL</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of products containing Paracetamol:</p> <p>WARNING</p> <div data-bbox="296 1599 1398 1751" style="border: 1px solid black; padding: 10px; margin: 10px 0;"> <p style="text-align: center;">This preparation contains PARACETAMOL.</p> <p>Do not take any other paracetamol containing medicines at the same time.</p> </div>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
103.	<p>PARACETAMOL WITH CAFFEINE IN COMBINATION</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of products containing Paracetamol with Caffeine in combination:</p> <p>WARNING</p> <ul style="list-style-type: none"> • Avoid other caffeine containing products. Too much caffeine may cause rapid heart rate, nervousness or sleeplessness. • Ask a doctor or pharmacist before use if you have high blood pressure, glaucoma, or overactive bladder syndrome. • DO NOT exceed 8 tablets in 24 hours. • DO NOT take more than the recommended dose unless advised by your doctor. Use the smallest effective dose. Taking more than the maximum daily dose may cause severe or possibly fatal liver damage. • DO NOT use with other drugs containing paracetamol. • NOT recommended for children under 12 years
104.	<p>PELARGONIUM SIDOIDES</p> <p>The following <u>warning</u> shall be <u>included on the labels and in the package inserts</u> of products containing <i>Pelargonium Sidoides</i>:</p> <p>WARNING</p> <p>In very rare cases, <i>pelargonium sidoides</i> may cause hypersensitivity reactions.</p>
105.	<p>PENICILLIN</p> <p>The following <u>statement</u> shall be <u>included on the labels</u> of products containing penicillin:</p> <p>‘Not to be used in patients with known hypersensitivity to Penicillin’</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
106.	<p>PHENIRAMINE</p> <p>The following <u>statement</u> shall be <u>included on the label and in the package inserts</u> of liquid oral products containing Pheniramine:</p> <p>WARNING</p> <p>When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>
107.	<p>PHENYLEPHRINE</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package insert</u> of liquid oral products containing Phenylephrine:</p> <p>WARNING</p> <p>When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>
108.	<p>PIRIBEDIL</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
109.	<p>PIROXICAM</p> <p>The following <u>additional information</u> shall be <u>included in the package inserts</u> of products containing Piroxicam:</p> <p>WARNING AND PRECAUTION</p> <ul style="list-style-type: none"> • Treatment should always be initiated by a physician experienced in the treatment of rheumatic diseases. • Use the lowest dose (no more than 20mg per day) and for the shortest duration possible. Treatment should be reviewed after 14 days. • Always consider prescribing a gastro-protective agent. <p>CONTRAINDICATION</p> <ul style="list-style-type: none"> • Piroxicam should not be prescribed to patient who is more likely to develop side effects, such as those with a history of gastro-intestinal disorders associated with bleeding, or those who have had skin reactions to other medicines. • Piroxicam should not be prescribed in association with any other NSAID or an anticoagulant. <p><i>Reference: Circular Bil (80) dlm BPFK/02/5/1.3: Menghadkan Indikasi bagi Produk untuk Kegunaan Systemic yang Mengandung Piroxicam kepada 'For the symptomatic relief of pain and inflammation in patients with osteoarthritis, rheumatoid arthritis and ankylosing spondylitis' dan Tambahan Amaran dan Kontraindikasi terkini pada sisip bungkus</i></p>
110.	<p>PRAMIPEXOLE</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
111.	<p>PROMETHAZINE HCL</p> <p>The following <u>additional information</u> shall be <u>included on the label and in the package insert</u> of liquid oral products containing Promethazine HCl:</p> <p>WARNING</p> <p>When used for treatment of cough and cold</p> <p>(a) “It (brand or generic names) should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression”.</p> <p>(b) To be used with caution and doctor’s/ pharmacist’s advice in children 2 to 6 years of age.</p> <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkus Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>
112.	<p>PROPAFENONE</p> <p>The following <u>warning</u> shall be <u>included in the package insert</u> of products containing propafenone:</p> <p>Propafenone is not recommended for treatment of less severe arrhythmias such as nonsustained ventricular tachycardias or frequent premature ventricular contractions even if the patients are symptomatic, because of recent evidence in the US of increase mortality in patients with non-lifethreatening arrhythmias who were treated with encainide and flecainide.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
113.	<p>PROPOFOL</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Propofol:</p> <p>WARNING</p> <p>Propofol is not recommended for paediatric general anaesthesia and sedation because its safety and effectiveness in these patients have not been established. There have been recent reports of adverse cardiac events and deaths associated with its use in paediatric intensive care. Although there is no evidence of a causal link of death with propofol in these cases, the drug could not be ruled out as a contributing factor. Until further data establishing its safety and delineating its appropriate dose range are available, propofol should not be used in paediatric intensive care.</p> <p>There have been very rare reports of epileptiform movement in epileptics and non-epileptics occurring during induction or emergence from anaesthesia induced by propofol.</p>
114.	<p>PROPOLIS (TOPICAL)</p> <p>The following <u>information</u> shall be <u>included on the labels and/ or package inserts</u> of products containing Propolis (for topical use):</p> <p>WARNINGS</p> <p>Propolis may cause allergic skin reaction.</p> <p>Reference:</p> <ul style="list-style-type: none"> a) Circular Bil (48) dlm BPFK/02/5/1.3: Pernyataan Amaran Pada Label Dan Sisip Bungkusan Produk Yang Mengandung Propolis (Topikal) dan Royal Jelly (Semua Bentuk) b) Bil (56) dlm BPFK/02/5/1.3: Pernyataan Amaran pada Label dan Sisip Bungkusan Produk yang Mengandung Propolis (topikal) dan Royal Jelly (Semua Bentuk)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
115.	<p data-bbox="276 300 611 333">PROPYLTHIOURACIL</p> <p data-bbox="276 371 1409 445">115.1 The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing propylthiouracil:</p> <p data-bbox="384 481 855 515">¹WARNING AND PRECAUTION</p> <p data-bbox="384 519 1409 775">Potential risk of serious hepatotoxicity or liver injury including liver failure and death. Patients who are initiated with propylthiourasil should be closely monitored for signs and symptoms of liver injury (e.g. fatigue, weakness, vague abdominal pain, loss of appetite, itching, easy bruising or yellowing of the eyes or skin) especially during the first six months. If liver injury is suspected, promptly discontinue propylthiouracil therapy.</p> <p data-bbox="384 801 1409 875">Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of the alternatives available.</p> <p data-bbox="276 902 1409 976">115.2 ²The following <u>boxed warning</u> shall be <u>included in the package inserts</u> of products containing propylthiouracil:</p> <div data-bbox="352 999 1385 1671" style="border: 1px solid black; padding: 10px;"> <p data-bbox="368 1010 655 1043">BOXED WARNING</p> <p data-bbox="368 1070 1369 1216"><i>Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.</i></p> <p data-bbox="368 1243 1369 1388"><i>Propylthiouracil should be reserved to patients who cannot tolerate carbimazole/ methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for management of hyperthyroidism.</i></p> <p data-bbox="368 1415 1369 1561"><i>Because of the risk of fetal abnormalities associated with carbimazole/ methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (See Warnings & Precautions).</i></p> </div> <p data-bbox="276 1711 421 1740">Reference:</p> <p data-bbox="276 1742 1409 1834">Circular ¹Bil (41) dlm. BPFK/PPP/01/03: <i>Kenyataan Amaran Berkaitan Dengan “Potential for an Increase in Risk of Hepatotoxicity” yang Perlu Dimuatkan Pada Sisip Bungkus Produk Propylthiouracil</i></p> <p data-bbox="276 1861 1409 1953">Circular ²Bil (55) dlm. BPFK/PPP/01/03: <i>Kenyataan Amaran Berbentuk “Boxed Warning” Yang Wajib Dimuatkan Pada Sisip Bungkus Produk Propylthiouracil Dengan “Severe Liver Injury”</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
116.	<p>PSEUDOEPHEDRINE</p> <p>The following <u>statement</u> shall be <u>included on the labels and in the package inserts</u> of liquid oral products containing Pseudoephedrine:</p> <p>WARNING When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>
117.	<p>PSYCHOTROPIC PRODUCTS</p> <p>The following <u>statement</u> shall be <u>included conspicuously on the labels</u> of all psychotropic products:</p> <p>CAUTION: This preparation may be habit forming on prolonged use.</p>
118.	<p>QUETIAPINE</p> <p>Please refer to ANTIPSYCHOTIC AGENT</p>
119.	<p>QUINAGOLIDE</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>
120.	<p>RISPERIDONE</p> <p>Please refer to ANTIPSYCHOTIC AGENT</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
121.	<p>ROPIRINOLE</p> <p>Please refer to DOPAMINERGIC INGREDIENT</p>
122.	<p>ROSIGLITAZONE</p> <p>122.1 The following <u>black boxed warning</u> shall be <u>included in the package inserts</u> of products containing Rosiglitazone as single ingredient or in combination with other active ingredients :</p> <div data-bbox="292 725 1399 1265" style="border: 1px solid black; padding: 10px;"> <ul style="list-style-type: none"> • Rosiglitazone is contraindicated in patients with established NYHA Class I to IV heart failure and in patients with known ischaemic heart disease, particularly in those taking nitrates. • Thiazolidinediones, including rosiglitazone, cause or exacerbate congestive heart failure in some patients. Patients on rosiglitazone should be monitored carefully for signs and symptoms of heart failure (including excessive, rapid weight gain, dyspnea, and/or edema). If these signs and symptoms develop, the heart failure should be managed according to current standards of care. Furthermore, discontinuation or dose reduction of rosiglitazone must be considered. </div> <p>122.2 The following information shall be <u>included in the package inserts</u> of products containing Rosiglitazone as single ingredient or in combination with other active ingredients :</p> <p>CONTRAINDICATIONS</p> <p>Rosiglitazone is contraindicated in patients with NYHA Class I to IV heart failure or history of cardiac failure, patients with known ischaemic heart disease and patients with Acute Coronary Syndrome (unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction.</p> <p>WARNING & PRECAUTIONS</p> <p>Rosiglitazone has been shown to be associated with an increased risk of myocardial ischaemia (angina, infarction) in pooled short term clinical studies compared to combined active/placebo control (2.00% versus 1.53%). Death from myocardial ischaemic events occurred in 0.15% on rosiglitazone – containing regimens and 0.12% on comparator regimen.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p>Reference: <i>Circular Bil (6) dlm BPFK/PPP/01/03 Jld 1: Direktif Memperketatkan Penggunaan Rosiglitazone dan Memperkukuhkan Amaran Berkaitan Dengan Risiko Kesan Advers Kardiovaskular Pada Sisip Bungkusan Semua Produk Rosiglitazone Termasuk Produk Kombinasi</i></p>
123.	<p>ROYAL JELLY</p> <p>The following <u>information</u> shall be <u>included</u> on the <u>labels</u> and/or <u>package inserts</u> of products containing Royal jelly:</p> <p>WARNINGS</p> <p>This product contains royal jelly and may cause severe allergic reactions including fatal anaphylactic reactions in susceptible individuals. Asthma and allergy sufferers may be at the greater risk.</p> <p>Reference:</p> <ul style="list-style-type: none"> a) Circular Bil (48) dlm BPFK/02/5/1.3: Pernyataan Amaran Pada Label Dan Sisip Bungkusan Produk Yang Mengandungi Propolis (Topikal) dan Royal Jelly (Semua Bentuk) b) Circular Bil (56) dlm BPFK/02/5/1.3: Pernyataan Amaran pada Label dan Sisip Bungkusan Produk yang Mengandungi Propolis (topikal) dan Royal Jelly (Semua Bentuk) c) Circular Bil (12) dlm. BPFK/PPP/01/03: Pernyataan amaran pada label dan sisip bungkusan produk yang mengandungi royal jelly (produk kosmetik)

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
124.	<p data-bbox="276 300 507 336">SALBUTAMOL</p> <p data-bbox="276 371 1409 450">124.1 The following information shall be included in the <u>package inserts</u> of products containing Salbutamol in <u>injection</u> dosage form:</p> <ul data-bbox="384 472 1409 1240" style="list-style-type: none"> <li data-bbox="384 472 1409 719">• As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. <li data-bbox="384 752 1409 999">• Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. <li data-bbox="384 1032 1409 1240">• Cautious use of salbutamol injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid interference with uterine contractility. During IV infusion of salbutamol, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute. <p data-bbox="276 1279 1409 1402">124.2 The following information shall be included in the <u>package inserts and product literature</u> of products containing Salbutamol in <u>oral tablet/capsule</u> dosage form:</p> <ul data-bbox="432 1424 1409 2007" style="list-style-type: none"> <li data-bbox="432 1424 1409 1715">• As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. <li data-bbox="432 1749 1409 2007">• Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology.

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p>124.3 The following <u>warning statement</u> shall be <u>included in the package inserts</u> of products containing Salbutamol in <u>injection and oral</u> dosage form under section of Warning & Precautions:</p> <p>Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration.</p> <p>Reference:</p> <ul style="list-style-type: none"> a) Circular Bil (6) dlm. BPFK/PPP/01/03: Kenyataan Amaran Mengenai Insiden Myocardial Ischaemia pada Wanita Mengandung yang Menerima Rawatan Beta Agonist bagi Rawatan Melambatkan Kelahiran Prematang pada Sisip Bungkusan Kumpulan Produk Ini b) Circular Bil (18) dlm BPFK/PPP/01/03 Jld 1: Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Risiko Kesan Advers Serius pada Jantung Termasuk Kematian dengan Penggunaan Produk Suntikan dan Oral Beta Agonis dalam Rawatan Kelahiran Pra-Matang

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
125.	<p>SEDATIVE – HYPNOTIC PRODUCTS</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> under section on 'Warning' and 'Precaution' of products containing:</p> <ol style="list-style-type: none"> Alprazolam Bromazepam Clobazam Diazepam Flurazepam hydrochloride Lorazepam Midazolam Nitrazepam Triazolam Zolpidem tartrate Zopiclone <p>WARNING/ PRECAUTION</p> <div style="border: 1px solid black; padding: 10px; margin: 10px 0;"> <ul style="list-style-type: none"> Anaphylaxis (severe allergic reaction) and angioedema (severe facial swelling) which can occur as early as the first time the product is taken Complex sleep – related behaviors which may include sleep driving, making phone calls, preparing and eating food while asleep </div> <p><i>Reference: Circular Bil (75) dlm BPFK/02/5/1.3: Pernyataan Amaran Pada Sisip Bungkus Semua Produk Sedatif-Hipnotik Oral Berkaitan dengan Risiko Complex Sleep - Related Behaviors Which May Include Sleep Driving, Making Phone Calls, Preparing and Eating Food (While Asleep)</i></p>
126.	<p>SELENIUM SULPHIDE</p> <p>The following <u>statement</u> shall be <u>included on the labels</u> of products containing Selenium sulphide:</p> <p>WARNING</p> <p>Do not use on broken skin or inflamed. Avoid contact with eyes.</p> <p>(AMARAN: Selenium sulphide tidak boleh digunakan pada kulit yang pecah dan radang. Elakkan daripada terkena mata.)</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
127.	<p>SENNA LEAF (<i>CASSIA</i>) AND <i>RHUBARB/ RADIX et RHIZOMA RHEI</i></p> <p>The following <u>statement</u> shall be <u>included on the labels</u> of products containing senna leaf (<i>cassia</i>) and <i>rhubarb/ radix et rhizoma rhei</i>:</p> <ul style="list-style-type: none"> • Do not use when abdominal pain, nausea or vomiting are present • Frequent or prolong use of this preparation may result in dependence towards the product and 'Imbalanced electrolytes'
128.	<p>SODIUM METABISULPHITE (EXCIPIENT)</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Sodium metabisulphite:</p> <p>WARNING</p> <p>This preparation contains Sodium metabisulphite that may cause serious allergic type reactions in certain susceptible patients. Do not use if known to be hypersensitive to bisulphites.</p>
129.	<p>SODIUM VALPROATE</p> <p>The following <u>boxed warning</u> shall be <u>included in the package inserts</u> of products containing Sodium valproate:</p> <div data-bbox="293 1375 1407 1877" style="border: 1px solid black; padding: 10px;"> <p>PANCREATITIS:</p> <p>CASES OF LIFE-THREATENING PANCREATITIS HAVE BEEN REPORTED IN BOTH CHILDREN AND ADULTS RECEIVING VALPROATE. SOME OF THE CASES HAVE BEEN DESCRIBED AS HEMORRHAGIC WITH A RAPID PROGRESSION FROM INITIAL SYMPTOMS TO DEATH. CASES HAVE BEEN REPORTED SHORTLY AFTER INITIAL USE AS WELL AS AFTER SEVERAL YEARS OF USE. PATIENTS AND GUARDIANS SHOULD BE WARNED THAT ABDOMINAL PAIN, NAUSEA, VOMITING, AND/OR ANOREXIA CAN BE SYMPTOMS OF PANCREATITIS THAT REQUIRE PROMPT MEDICAL EVALUATION. IF PANCREATITIS IS DIAGNOSED, VALPROATE SHOULD BE DISCONTINUED.</p> </div>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
130.	<p>ST. JOHN'S WORT (<i>Hypericum perforatum</i>)</p> <p>The following <u>boxed statement</u> shall be <u>included on the labels</u> of products containing St. John's Wort:</p> <div data-bbox="288 477 1396 808" style="border: 1px solid black; padding: 10px; margin: 10px 0;"> <p>Please consult your physician/ pharmacist before using this product if you are on any prescription medicines as there is possibility that interactions may occur with certain drugs.</p> <p><i>(Sila dapatkan nasihat doktor/ ahli farmasi sebelum menggunakan produk ini, kerana kemungkinan berlakunya interaksi dengan penggunaan ubat perikripsi).</i></p> </div>
131.	<p>STATINS</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing statins:</p> <ol style="list-style-type: none"> a. Atorvastatin b. Cerivastatin c. Cilastatin d. Fluvastatin e. Lovastatin f. Pravastatin g. Simvastatin h. Somatostatin i. etc. <p>DRUG INTERACTION: Concurrent use of fibrates may cause severe myositis and myoglobinuria.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
132.	<p data-bbox="284 300 831 336">SULPHONAMIDES/ TRIMETHOPRIM</p> <p data-bbox="284 371 1407 479">132.1 The following <u>statement</u> shall be <u>included on the labels</u> of products containing Sulphonamides and Trimethoprim as single ingredient or in combination of both ingredients:</p> <div data-bbox="309 492 1401 636" style="border: 1px solid black; padding: 10px;"> <p data-bbox="325 519 1385 591">Discontinue treatment with this drug immediately if skin rash or any sign of adverse reaction occurs.</p> </div> <p data-bbox="284 685 1407 792">132.2 The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Sulphonamides and Trimethoprim as single ingredient or in combination of both ingredients:</p> <div data-bbox="309 806 1401 1075" style="border: 1px solid black; padding: 10px;"> <p data-bbox="325 837 1385 1016">Fatalities associated with the administration of sulphonamides and trimethoprim, either alone or in combination, have occurred due to severe reactions, including Steven-Johnson syndrome, toxic epidermal necrolysis and other reactions. The drug should be discontinued at the first appearance of skin rash or any sign of adverse reaction.</p> </div>
133.	<p data-bbox="284 1196 507 1232">TERBUTALINE</p> <p data-bbox="284 1267 1407 1339">133.1 The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Terbutaline in <u>injection</u> dosage form:</p> <ul data-bbox="395 1366 1407 2002" style="list-style-type: none"> <li data-bbox="395 1366 1407 1612">• As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. <li data-bbox="395 1644 1407 1890">• Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients's cardiovascular status should be made by a physician experienced in cardiology. <li data-bbox="395 1921 1407 2002">• Cautious use of terbutaline injections is required in pregnant patients when it is given for relief of bronchospasm so as to avoid

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p>interference with uterine contractility. During IV infusion of terbutaline, the maternal pulse should be monitored and not normally allowed to exceed a steady rate of 140 beats per minute.</p> <p>133.2 The following information shall be included in the <u>package insert and product literature</u> of products containing Terbutaline in <u>oral tablet/capsule</u> dosage form:</p> <ul style="list-style-type: none"> • As maternal pulmonary oedema and myocardial ischaemia have been reported during or following premature labour in patients receiving beta2 – agonists, careful attention should be given to fluid balance and cardio-respiratory function, including ECG monitoring. If signs of pulmonary oedema and myocardial ischaemia develop, discontinuation of treatment should be considered. • Due to the risk of pulmonary oedema and myocardial ischaemia that has been observed during the use of beta2-agonists in the treatment of premature labour, before these products are given to any patient with known heart disease, an adequate assessment of the patients' cardiovascular status should be made by a physician experienced in cardiology. <p>133.3 The following <u>warning statement</u> shall be included in the <u>package inserts</u> of products containing Salbutamol in <u>injection and oral</u> dosage form under section of Warning & Precautions:</p> <ul style="list-style-type: none"> • Tocolysis: Serious adverse reactions including death have been reported after administration of terbutaline/ salbutamol to women in labor. In the mother, these include increased heart rate, transient hyperglycaemia, hypokalaemia, cardiac arrhythmias, pulmonary oedema and myocardial ischaemia. Increased fetal heart rate and neonatal hypoglycaemia may occur as a result of maternal administration. <p>Reference:</p> <ol style="list-style-type: none"> a) Circular Bil (6) dlm. BPFK/PPP/01/03: Kenyataan Amaran Mengenai Insiden Myocardial Ischaemia pada Wanita Mengandung yang Menerima Rawatan Beta Agonist bagi Rawatan Melambatkan Kelahiran Prematang pada Sisip Bungkusan Kumpulan Produk Ini b) Circular Bil (18) dlm BPFK/PPP/01/03 Jld 1: Direktif untuk Memperkukuhkan Amaran Berkaitan dengan Risiko Kesan Advers Serius pada Jantung Termasuk Kematian dengan Penggunaan Produk Suntikan dan Oral Beta Agonis dalam Rawatan Kelahiran Pra-Matang

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
134.	<p>TETRACYCLINE SYRUP</p> <p>The following <u>boxed warning</u> shall be <u>included on the label and in the package inserts</u> of products containing Tetracycline (syrup)</p> <div data-bbox="296 490 1393 577" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>NOT TO BE GIVEN TO CHILDREN UNDER 12 YEARS OF AGE</p> </div>
135.	<p>THIOMERSAL</p> <p><u>Note:</u> Thiomersal is not allowed in ophthalmic preparations as preservative.</p> <p>The following <u>statement</u> shall be <u>included on the label and package inserts</u> of products containing thiomersal for preparations other than ophthalmic preparation:</p> <p>WARNING</p> <p>‘RISK OF SENSITIZATION IN RELATION TO THIOMERSAL AND OTHER PRESERVATIVES’</p> <p><i>Reference: Circular Bil (34)d/m BPFK/02/5/1.3: Penggunaan Thiomersal Dalam Persediaan Vaksin</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
136.	<p>THROMBOLYTIC AGENTS</p> <p>The following <u>caution</u> shall be <u>disclosed prominently in the package inserts</u> of products containing “systemic thrombolytic agent” in particular “the tissue plasminogen activators”:</p> <p>WARNING</p> <p>Severe bleeding such as intracranial haemorrhage may occur following administration of the drug, particularly in the elderly patients. The risk must be balanced against the potential benefit of thrombolysis.</p> <p>The following precautions need to be observed: Patients should be carefully observed for clinical signs during and following administration of the drug for early detection of bleeding. Frequent haematological tests such as blood coagulation tests are mandatory.</p> <p>To prevent bleeding at the site of centesis or other regions, caution must be exercised concerning procedures and management of arterial/ venus puncture.</p> <p>The use of heparin in conjunction with the thrombolytic agent for the purpose of prevention of reocclusion may increase the risk of intracranial haemorrhage. Close monitoring of patients is strongly recommended.</p>
137.	<p>TIAPROFENIC ACID</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Tiaprofenic acid:</p> <p>PRECAUTION</p> <p>Urinary symptoms (bladder pain, dysuria, and frequency), haematuria or cystitis may occur. In certain exceptional cases, the symptoms have become severe on continued treatment. Should urinary symptoms occur, treatment with tiaprofenic acid must be stopped.</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
138.	<p>TRETINOIN TOPICAL</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Tretinoin used topically:</p> <p>USE IN PREGNANCY:</p> <div style="border: 1px solid black; padding: 10px; margin-top: 10px;"> <p>Studies in animal have shown that oral tretinoin is fetotoxic in rats given 500 times the topical human dose and teratogenic in rats given 1,000 times the topical human dose. Topical tretinoin has caused delayed ossification in a number of bones in the offspring of rats and rabbits given 100 to 320 times the topical human dose, respectively. There has been increasing incidence of foetal malformation following topical administration of tretinoin. Use of topical tretinoin is not recommended during pregnancy, especially the first trimester.</p> </div>
139.	<p>TRIAZOLAM</p> <p>Please refer to SEDATIVE – HYPNOTIC PRODUCTS</p>
140.	<p>TRIMETAZIDINE</p> <p>140.1 Indication of products containing Trimetazidine shall be amended as follows:</p> <ol style="list-style-type: none"> a) Indication of Trimetazidine for treatment of pectoris angina is limited to second-line add on therapy; and the indication in otology and ophthalmology field shall be removed. b) Permitted indication is <i>trimetazidine is indicated in adults as add-on therapy for the symptomatic treatment of patients with stable angina pectoris who are inadequately controlled by or intolerant to first-line antianginal therapies.</i> <p>140.2 The following <u>warning statement</u> shall be <u>included in the package inserts</u> of products containing Trimetazidine:</p> <ol style="list-style-type: none"> a) At part of <i>Dosage and method of administration:</i> <u>For products containing Trimetazidine 20mg:</u> <i>The dose is one tablet of 20mg of trimetazidine three times a day during meals.</i>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p><i>The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.</i></p> <p><u>Special populations</u></p> <p><i>Patients with renal impairment:</i> <i>In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals.</i></p> <p><i>Elderly patients:</i> <i>Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 20mg twice daily, i.e., one in the morning and one in the evening during meals. Dose titration in elderly patients should be exercised with caution.</i></p> <p><u>For products containing Trimetazidine 35mg:</u></p> <p><i>The dose is one tablet of 35mg of trimetazidine twice daily during meals.</i></p> <p><i>The benefit of the treatment should be assessed after three months and trimetazidine should be discontinued if there is no treatment response.</i></p> <p><u>Special populations</u></p> <p><i>Patients with renal impairment:</i> <i>In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast.</i></p> <p><i>Elderly patients:</i> <i>Elderly patients may have increased trimetazidine exposure due to age-related decrease in renal function. In patients with moderate renal impairment (creatinine clearance [30-60] ml/min), the recommended dose is 1 tablet of 35mg in the morning during breakfast. Dose titration in elderly patients should be exercised with caution.</i></p> <p>b) At part of Contraindications:</p> <ul style="list-style-type: none"> - <i>Parkinson disease, parkinsonian symptoms, tremors, restless leg syndrome, and other related movement disorders</i> - <i>Severe renal impairment (creatinine clearance < 30ml/min).</i>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
	<p>c) At part of Special warnings and precautions for use:</p> <p><i>Trimetazidine can cause or worsen parkinsonian symptoms (tremor, akinesia, hypertonia), which should be regularly investigated, especially in elderly patients. In doubtful cases, patients should be referred to a neurologist for appropriate investigations.</i></p> <p><i>The occurrence of movement disorders such as parkinsonian symptoms, restless leg syndrome, tremors, gait instability should lead to definitive withdrawal of trimetazidine.</i></p> <p><i>These cases have a low incidence and are usually reversible after treatment discontinuation. The majority of the patients recovered within 4 months after trimetazidine withdrawal. If parkinsonian symptoms persist more than 4 months after drug discontinuation, a neurologist opinion should be sought.</i></p> <p><i>Falls may occur, related to gait instability or hypotension, in particular in patients taking antihypertensive treatment.</i></p> <p><i>Caution should be exercised when prescribing trimetazidine to patients in whom an increased exposure is expected:</i></p> <ul style="list-style-type: none"> - moderate renal impairment, - elderly patients older than 75 years old. <p>d) At part of Side effects:</p> <p>Nervous system disorders:</p> <p>Frequency not known: <i>Parkinsonian symptoms (tremor, akinesia, hypertonia), gait instability, restless leg syndrome, other related movement disorders, usually reversible after treatment discontinuation.</i></p> <p>Reference: Directive No. 5 Year 2013, (4)dlm.BPFIK/PPP/07/25: Direktif untuk menghadkan penggunaan produk mengandung Trimetazidine dan mengukuhkan amaran berkaitan dengan risiko kesan advers simptom parkinson pada sisip bungkusan semua produk Trimetazidine</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
141.	<p>TRIPROLIDINE</p> <p>The following <u>statement</u> shall be <u>included on the label and in the package inserts</u> of liquid oral products containing Triprolidine:</p> <p>WARNING</p> <p>When used for treatment of cough and cold:</p> <ul style="list-style-type: none"> (a) Not to be used in children less than 2 years of age (b) To be used with caution and doctor's/ pharmacist's advice in children 2 to 6 years of age. <p><i>Reference: Circular Bil (34) dlm. BPFK/PPP/01/03: Kenyataan Amaran Pada Label dan Sisip Bungkusan Produk Persediaan Cecair Oral Untuk Rawatan Batuk dan Selsema (Cough and Cold) yang Mengandungi Antihistamin, Antitusif dan Dekongestan (Sebagai Bahan Aktif Tunggal atau Kombinasi)</i></p>
142.	<p>VARENICLINE</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Varenicline:</p> <p>SPECIAL WARNINGS AND PRECAUTIONS FOR USE</p> <p><u>Effect of smoking cessation:</u></p> <p>Smoking cessation, with or without pharmacotherapy has been associated with the exacerbation of underlying psychiatric illness (eg. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.</p> <p>Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt.</p> <p>UNDESIRABLE EFFECTS</p> <p>Post marketing cases of MI, depression and suicidal ideation have been reported in patients taking varenicline.</p> <p><i>Reference: Circular Bil (83) dlm. BPFK/17/FV/28: Maklumat dari European Medicines Agency (EMA) berkaitan penggunaan produk Champix (Varenicline) untuk rawatan berhenti merokok (smoking cessation).</i></p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
143.	<p>VITAMIN K</p> <p>142.1 The following statement shall be included in the label and package insert of health supplement products containing Vitamin K as combined ingredients with other vitamins and minerals in oral preparation:</p> <div data-bbox="368 506 1404 640" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>‘Consult a healthcare practitioner if you are on anticoagulant/ blood thinner products.</p> </div> <p>142.2 The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Vitamin K1 (phytomenadione) as single ingredient used intravenously:</p> <p>WARNING Severe reactions, including fatalities, have occurred during and immediately after intravenous injection of Vitamin K1. Restrict intravenous use to emergency case. When intravenous administration is necessary, the rate of injection should not exceed 1mg per minute.</p> <p>ADMINISTRATION: In severe bleeding, or situations where other routes are not feasible, Vitamin K1 may be given by very slow intravenous injection, at a rate not exceeding 1mg per minute.</p>
144.	<p>WARFARIN</p> <p>The following <u>statement</u> shall be <u>included in the package inserts</u> of products containing Warfarin:</p> <p>CAUTION Topical preparations containing methyl salicylate should be used with care in patients on Warfarin and excessive usage is to be avoided as potentially dangerous drug interaction can occur.</p>
145.	<p>ZIPRASIDONE</p> <p>Please refer to ANTIPSYCHOTIC AGENT</p>

NO.	SPECIFIC LABELLING REQUIREMENTS (SUBSTANCE SPECIFIC)
146.	ZOLPIDEM TARTRATE Please refer to SEDATIVE – HYPNOTIC PRODUCTS
147.	ZOPICLONE Please refer to SEDATIVE – HYPNOTIC PRODUCTS

APPENDIX 10

GUIDELINE ON PATIENT DISPENSING PACK FOR PHARMACEUTICAL PRODUCTS IN MALAYSIA

Outline:

- 10.1 Purpose
- 10.2 Objective
- 10.3 Definition
- 10.4 Benefits
- 10.5 Criteria for Implementation of Patient Dispensing Pack
- 10.6 Products Exempted from this Requirements
- 10.7 Other Considerations for Implementation
- 10.8 Implementation Timeline
- 10.9 Conclusion

10.1 PURPOSE

To provide guidance on the implementation of patient dispensing pack or original dispensing pack for pharmaceutical products in Malaysia.

10.2 OBJECTIVE

Improve patient's safety by:

- maintaining product integrity;
- prevent unnecessary exposure of the product;
- avoid product contamination due to handling especially in non-GMP premise; and
- Fewer steps in dispensing process hence less possibility for errors and improvement in efficiency.

10.3 DEFINITION

Patient dispensing pack or original dispensing pack is a ready-to-dispense pack with sufficient quantity equivalent to an amount not more than one month supply or per treatment for one patient's use.

10.4 BENEFITS

Key benefits identified:

- Ensuring patients on how to take medications and the importance of it, which will eventually increase patient's compliance.
- Clear identification of the medicine, by whom and where it was manufactured.
- Providing complete instructions on the use of the medicine.
- Original packing will maintain the integrity of the pack therefore ensuring the stability of the product.
- Original packing will carry batch number and expiry date.
- Prevent mix-ups (or contamination) during repacking and dispensing.
- Facilitate recall of products since the required information can only be found on the original pack.

10.5 CRITERIA FOR IMPLEMENTATION OF PATIENT DISPENSING PACK

- The patient dispensing pack size should be based on the medication, intended use, recommended dosage and dosage form sufficient for one month supply or per treatment for one patient's use.
- This requirement does not apply for blister or strip pack.
- Maximum permitted supply is one month but may be less depending on the intended use of the medication.
- The Product Registration Holder (PRH) is responsible to justify the proposed patient dispensing pack size based on these criteria as the dosing regimen for certain medication may equate to high numbers of tablets/ capsules. Justification should also address the definition of one month i.e. 28, 30 or 31 days.
- Blister or strip pack are strongly recommended for solid oral dosage forms (e.g. tablets and capsules) and bulk loose pack for supply more than one month are not permitted unless justified by the PRH.
- Oral chemotherapeutics in tablet or capsule must be packed in blister to reduce personnel exposure and presumably risk which can minimise the toxic effect of the chemotherapeutics.

10.6 PRODUCTS EXEMPTED FROM THIS REQUIREMENTS

The requirements do not apply to the following products:

- Injectables, eye, ear and nasal drops, suppositories and pessaries.
- Products for export only (FEO).
- Drug where the risk of issuing more than the amount required by the patient outweigh the benefits of the patient dispensing pack e.g. products containing substances with potential for abuse or cytotoxic agents where precise dosing are required.
- Drugs where the dosing needs to be tailored according to patient's body weight e.g. drugs used in oncology, HIV etc.
- Medically critical products and hospital packs for rare diseases with very low volumes where it is not viable to produce special packs for a single market.
- Products sold with devices with a fixed number of doses
- Situations where a patient dispensing pack is not appropriate will be considered on a case to case basis.

10.7 OTHER CONSIDERATIONS FOR IMPLEMENTATION

VARIATION APPLICATIONS

- Change in patient pack size with or without involving new pack type shall be submitted to Variation Section, Centre for Post Product Registration.
- Supporting documents required are:
 - a. Justification for the new pack size and/or type;
 - b. Accelerated stability data (3 or 6 months) and stability report for new pack types; and
 - c. Commitment to provide complete real time stability data and report when available.
- List of products with recommended pack sizes for oral liquid preparations and dermatological are as in **Table 1** and **Table 2** respectively.
- For tablets and capsules in loose pack, the maximum packing size will depend on the highest dosage and frequency per patient's treatment or one month supply.

10.8 IMPLEMENTATION TIMELINE

- Implementation of patient dispensing pack has been conducted in a phased manner to ensure smooth transition while ensuring no supply disruption to patients. This implementation is effective since 1 March 2008 on a voluntary basis and mandated on 1 September 2008.
- All products manufactured from 1 September 2008 regardless whether it is imported or locally manufactured will need to conform to the principles of this guide.

10.9 CONCLUSION

Patient Dispensing Pack is convenient, safe and improves quality of dispensed medicines. It will increase efficiency in dispensing and improve safety by reducing the risk and possibility of error. It will also result in a reduction in drug waste and better use of resources.

TABLE 1:**Oral Liquid Preparation Maximum Pack Size Recommendations for Pharmaceutical Products**

ATC Code	Recommended Pack sizes
R05 Cough & cold preparation R05A Cold preparation R05C Antitussives R05D Expectorants	Max 120ml (except for Pholcodine – Max 90ml)
R06A Antihistamines systemic	Max 120ml (except for Hydroxyzine HCl Syrup - 200ml)
R03 Anti-asthma & COPD products R03A Beta2 stimulants R03B Xanthines (theophyllines) R03C Non-steroidal respiratory anti-inflammatory (ketotifen)	Max 120ml (except for Procaterol - 250ml)
N02B Non-narcotic analgesics	Max 120ml
M01A Antirheumatics non-steroid	Max 120ml
H02 Systemic corticosteroids H02A Plain corticosteroids	Max 120ml
M06A Anti-inflammatory enzymes	Max 500ml
A02A Antacid antiflatulents A02B Antiulcerants	Max 250ml
A06A Laxatives	Max 120ml (except for Lactulose - 500ml)
A03 Functional GI disorder drugs A03A Antispasmodic A03E Other GI combinations (Colimix) A03F Gastroprokinetics (Metoclopramide, Motilium) A07 Antidiarrhoea	Max 120ml

ATC Code	Recommended Pack sizes
A04A Antiemetic + Antinauseants N07C Antivertigo products	Max 120ml
N03A Antiepileptics	Max 250ml (Except for Sodium Valproate Syrup - 300ml)
N06A Antidepressant & Mood stabilizer N06D Anti Dementia N07D Anti-Alzheimer products N05A Antipsychotics	Max 250ml Max 20ml for drops
P01B Anthelmintics	Max 60ml
N05C Tranquillizers/ Anxiolytics	Max 250ml
A05B Hepatic protector – lipotropics	Max 150ml
J05 Antivirals for systemic use J05B Antivirals excluding Anti-HIV J05C HIV antivirals	Max 250ml
J01 Antibiotics systemic J01A Tetracyclines & combination J01B Chloramphenicols + combinations J01C1 Oral broad spectrum Penicillins J01D1 Oral Cephalosporins J01E Trimethoprim combinations J01F Macrolides & similar type J01H Medium & narrow spectrum penicillins J01X Other antibiotics J02A Systemic Antifungals Agents	Max 120ml
N06D Nootropics N06E Neurotonics & Miscellaneous	Max 125 ml
G01A1 Trichomonacides	Max 120ml

TABLE 2:

DERMATOLOGICALS PREPARATION MAXIMUM PACK SIZE
RECOMMENDATIONS FOR PHARMACEUTICAL PRODUCTS

ATC Code	Recommended Pack sizes
D01A Antifungals for topical use	Liquid preparation - max 250ml Others - max 60g
D02A Emollients and protectives	Non poisons (liquid preparation) - 250ml Others - 60g (max 500g for emollients) Except D02AC Soft paraffin and fat products and D02AX Other emollients and protectives (Aq. Cream) - max 500g
D03 Preparations for treatment of wounds and ulcers	Max 500ml to 1L <u>Notes:</u> <ul style="list-style-type: none"> ▪ Chlorhexidine gluconate aqueous 1L ▪ Povidon 10% 500ml ▪ Povidon-iodine 1L ▪ Dermacyn 500ml ▪ Hydrogen peroxide 1L ▪ Prontosan 500ml ▪ Octenisan 500ml ▪ Acetic acid 500ml ▪ Cetrimide 500ml
D04A Antipruritics, anesthetics, etc. Except D04AA Antihistamines for topical use (not allowed for registration)	Liquid – max 250ml Others – 60g

ATC Code	Recommended Pack sizes
D05A Antipsoriatics for topical use	Liquid – max 500ml (with a dispenser). Others – max *500g Bar – max 100g * <u>Notes:</u> <ul style="list-style-type: none"> ▪ Tar Preparations ▪ Coal Tar Ointment/ Solution ▪ Liquor Picis Carbonis (LPC) 500g ▪ Dithranol Ointment 500g ▪ Coccois Co Lotion 500ml
D06A Antibiotics for topical use	Max 20g Except D06BB Antivirals - Max 10g D06B A 01 Silver Sulphadiazine for management of burns - 500g
D07A Corticosteroids, plain D07AA Corticosteroids, weak (group I) D07AB Corticosteroids, moderately potent (group II) D07AC Corticosteroids, potent (group III) D07AD Corticosteroids, very potent (group IV)	D07AA – Max 100g to **500g D07AB – Max 50g to **500g D07AC – Max 15g to 100g D07AD – Max 15g to 100g ** <u>Note:</u> Pack size of 500g is for hospitals and skin specialist clinics use.

ATC Code	Recommended Pack sizes
D07C Corticosteroids, combinations with antibiotics	
D07CA Corticosteroids, weak, combinations with antibiotics	D07CA - Max 100g
D07CB Corticosteroids, moderately potent, combinations with antibiotics	D07CB - Max 50g
D07CC Corticosteroids, potent, combinations with antibiotics	D07CC - Max 15g
D07CD Corticosteroids, very potent, combinations with antibiotics	D07CD - Max 15g
D08A Antiseptics and disinfectants	Liquid antiseptics/ disinfectants - 1Litre Others - max 60g
D10A Anti-acne preparations for topical use Except for D10AA Corticosteroids, combinations for treatment of acne	Liquid preparation - max 250ml (recommended to be used with a dispenser) Bar - max 100g All others - max 60g
D11AF Wart and anti-corn preparations	Max 15ml
M02A Topical products for joint and muscular pain	Liquid – 250ml Others, Max – 60g
D11AX11 Hyperpigmentation	Max 60g

Reference: Circulars[\(bil 16\) dlm bpfk02/5/1.3.pdf](#)[Bil \(22\) dlm BPFK/02/5/1.3.pdf](#)[Bil \(21\) dlm.BPFK/02/5/1.3.pdf](#)[Bil \(24\) dlm BPFK/02/5/1.3.pdf](#)[\(1\) dlm. BPFK/02/5/1.4](#)[Bil \(4\) dlm BPFK/PPP/01/03 Jld 1](#)

APPENDIX 11:

GUIDELINE ON FILLING THE ONLINE APPLICATION FORM FOR PRODUCT REGISTRATION VIA QUEST SYSTEM

IMPORTANT NOTES:

Online application forms are available for different product categories in the QUEST system:

- a) Pharmaceuticals;
- b) Health Supplements and Natural Products.

This appendix may not follow the sequence of the online registration forms.

Applicant shall follow and comply with all requirements in the online application forms as well as any supplementary documentation requested by the Authority, whichever it may deems fit.

Applicant shall ensure that you have clicked on the appropriate section of the display panel and fill the correct application form.

Applicants are advised to read the explanatory notes in this appendix, as well as relevant ASEAN or ICH guidelines and checklists, for full information on requirement for product registration. In order to facilitate the evaluation process the Authority, applicants shall conform to these guidelines as well as the main guidance document.

The Authority reserves the right to request for supplementary information in certain cases.

Outline:

11.1 Product Classification

11.1.1 Pharmaceuticals

11.1.2 Health Supplements and Natural Products

11.2 Submission of Application

11.2.1 Step 1: Product Validation

11.2.2 Step 2: New Registration Application Form

Part I – Administrative Data and Product Information

- Section A: Product Particulars
- Section B: Product Formula
- Section C: Particulars of Packing
- Section D: Label (Mockup) for Immediate Container, Outer Carton and
Proposed Package Insert
- Section E/ Section F: Supplementary Documentation

Part II, III & IV – Quality , Nonclinical Document & Clinical Document

11.1 PRODUCT CLASSIFICATION

Applicant shall ensure correct product category as listed below in order to determine the method of evaluation i.e. full evaluation (*) or abridged evaluation (**) in which available as separate modules for application.

11.1.1 Pharmaceuticals

- i) New Drug Products *
- ii) Biologicals *
- iii) Generics (Scheduled Poison) *
- iv) Generics (Non-Scheduled Poison) (or known as OTC/ non-prescription) - *other than listed at v) **
- v) Generics (Non-Scheduled Poison) **, which include, but not limited to the following:
 - Antiseptics/ skin disinfectants;
 - Locally-acting lozenges/ pastilles;
 - Topical analgesic/ counter-irritants;
 - Topical nasal decongestants;
 - Emollient/ demulcent/ skin protectants;
 - Keratolytics;
 - Anti-dandruff;
 - Oral care;
 - Anti-acne;
 - Medicated plasters/ patch/ pad; and
 - Topical antibacterial.

11.1.2 Health Supplements and Natural Products **

- Application form for registration for Health Supplements; and Natural Products (or termed as Traditional Products) are available under Abridged module.
- Do not use the pharmaceuticals module for these product categories.

11.2 SUBMISSION OF APPLICATION

Any application for a product registration shall follow a 2-step process i.e. Step 1 (Product Validation) and Step 2, as described below:

11.2.1 STEP 1: PRODUCT VALIDATION

- All fields are compulsory to be entered.
- Option is given either to accept the validation result and submit; or override and manually select.
- Once validation is verified and submitted, the related application form under Step 2 will be displayed.
- Information entered in Step 1 will be captured in the database and need not be re-entered at Step 2.

[1] Product Name

- Product name, dosage form and strength shall be entered.
(e.g. X Brand Paracetamol Tablet 500mg)
- Product name is defined as a name given to a product which may be either a proprietary name (an invented name); or a generic name (common name) or scientific name, together with a trade mark or the name of the manufacturer.
- Product name shall not imply the following:
 - a. Tricky, confusive and against the law;
 - b. Scandalous and offensive;
 - c. Prejudicial;
 - d. Notorious.
- Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product or a product that has been revoked due to safety concerns is prohibited.
- The invented name shall not be liable to confusion with the common name.
- The generic name means the international non-proprietary name recommended by WHO (rINN), or if one does not exist, the usual approved name.
- The product name shall be shown on the product labelling i.e. immediate label, outer unit carton, package insert and patient information leaflet.
- Dosage form and strength of product would need to be entered as part of product name to allow for multiple dosage forms (e.g. tablet, capsule) and strengths (e.g. 200mg and 400mg) for any particular named (proprietary or generic) product.
- If a product name is found similar to another registered product or any other name which deemed inappropriate by the Authority, NPCB reserves the rights to request for the change of the product name.

[2] Dosage Form

- Please select dosage form and further select 'in the form of' from the drop-down list.
- For example, a tablet may be in the form of chewable, coated (enteric, film, or sugar), uncoated, dispersible, effervescent, extended release, sublingual, etc.
- The form that correctly describes it in terms of its product quality control specifications and performance shall be selected.
- A separate application for registration is required for each dosage form.

[3] Active Ingredients

i) Name of Active Ingredient:

- Please refer [Appendix 8.1](#) List of Prohibited and Restricted Active Ingredients and Combinations.
- Please select active ingredient from the search database by clicking button 'click here to search'. If an active ingredient is not listed in the database, please click button 'Not Listed Ingredient'. Automatic e-mail will be send to NPCB for verification. Please ensure that the spelling is accurate.
- The actual raw material that is employed in the manufacturing process shall be named. For example:
 - Where the raw material used is the salt (e.g. ampicillin trihydrate) which will yield an equivalent effective component from its base content (i.e. ampicillin), the substance name is the salt and the equivalent base component should be indicated in remarks on substance (if any) field. ***
 - Similarly where a chemical is a component in the ingredient (e.g. iron in ferrous sulfate; or EPA and DHA in fish oil), the component details shall be stated in the remarks field if a label claim of the component is made for the product, and the actual raw material used declared as the active ingredient.
- International Non-proprietary Names (INN), approved names, pharmacopoeia names of ingredients shall be used whenever possible.

- After each ingredient entry is correctly made, click the button 'add/save'. The button 'remove' will allow for corrections to an entry under this heading. To remove item, please select item from the listing and click 'remove'.

ii) Strength of active ingredient:

- Please enter strength of active ingredient (numerical) and then select unit weights and measures from the drop-down list.
- Content of ingredients shall be expressed as appropriate in the following manner :
 - a. quantity per dose unit
(e.g. for unit dose formulations - tablet, capsule, lozenge, etc.)
 - b. percentage composition - %w/w, %w/v, %v/v, etc.
(e.g. for products without defined dose unit such as ointments, creams, solutions, etc.)
 - c. weight per ml.
(e.g. for solutions, injections, etc.)
 - d. quantity (percentage or amount) per measured dose
(e.g. oral liquids, metered aerosols, drops, etc.)
- Metric weights and measures shall be used.
- In cases where product contains active ingredient(s) that cannot be definitely identified (e.g. certain biological products) state the name of the material to which activity is ascribed and, where appropriate, the potency or activity of the product.

iii) Remarks on active ingredient (if any).***

- This field shall be used where the raw material in product formulation yields an equivalent active component.

After each ingredient entry is correctly made, click the 'add/ save' button. The remove button will allow for corrections to an entry under this heading. To remove item, select item from the listing and click remove.

[4] Excipient

- Please refer [Appendix 8.2](#) List of Prohibited and Restricted Excipients; and Appendix 8.3 Lists of Permitted and Restricted Colouring Agents.
- Details are as for [3] Active Ingredients stated above.

- Please enter function of excipients, e.g. sweetener, preservative, thickening agent, etc. which can be selected from the drop-down list.

[5] Any Animal Origin

- Click the appropriate button 'Yes' or 'No'.

[6] Manufacturer

- **Definition of Manufacturer:** A company that carries out at least one step of production as well as the final release of the finished product.
- Click button 'click here to search' to select manufacturer listed in the database. For a new manufacturer which is not listed in the database search, please click 'Not Listed Manufacturer' button. Automatic e-mail will be send to NPCB for verification.

[7] Is The Selected Manufacturer a Contract Manufacturer?

- Status as to whether the declared manufacturer is a contract manufacturer or otherwise, has to be entered. Click the appropriate button 'Yes' or 'No'.

[8] Is This Product Second Source?

- Click the appropriate button 'Yes' or 'No'.
- If yes, please attach letter of declaration stating that this product is a second source product; and provide registration number and product name of the first source.

[9] Does This Product Contain Any Premix?

- Click the appropriate button 'Yes' or 'No'.
- If yes, please provide the following details:
 - i) State your premix form
 - j) Manufacturer name

- k) Manufacturer address
- l) Certificate of Good Manufacturing Practice (GMP)
- m) Formulation
- n) Manufacturing Process
- o) Specification of Analysis
- p) Certificate of Analysis (CoA)

[10] Is This a Replacement Product?

- Click the appropriate button 'Yes' or 'No'.
- If yes, please attach letter of declaration stating that this product is a replacement product; and provide registration number and product name of the replaced product.

[11] Other Manufacturer (Repacker)

- Click the appropriate button 'Yes' or 'No'.
- Please enter name of company and click button 'search' to select other manufacturer (repacker) listed in the database. For a new other manufacturer (repacker) which is not listed in the database search, please click 'Not Listed Manufacturer' button. Automatic e-mail will be send to NPCB for verification.
- Select from processing type drop-down list, e.g. assembly, packing, production, labelling, fill and finish, others.

[12] Is This an Imported Product?

- Click the appropriate button 'Yes' or 'No'.

11.2.2 STEP 2: NEW REGISTRATION APPLICATION FORM

Please click at 'Section List' button to display the application form at Step 2. The requirement displayed will depend on the category of product being selected for registration submission:

- Abridged Evaluation for certain **OTCs, health supplements and natural products;
- Generic Pharmaceutical Products - **Parts I & II**;
- Existing chemical or biological entity(s) in new dosage form - **Parts I & II together with pharmacokinetic data**;
- NDP and Biologics - **Parts I to Part IV**:
 - Part I - Administrative Data and Product Information
 - Part II - Quality
(For details of Part II, please refer Section C: Quality Control in the main DRGD)
 - Part III - Nonclinical Document
 - Part IV - Clinical Document.

Please refer [Glossary developed for the ACTD and ACTR](#). The definitions used in the glossary have been developed for the ASEAN Common Technical Dossier (ACTD) and Common Technical Requirements (ACTR). They are not necessarily meaningful outside the scope of the specific parts of ACTD and ACTR to which they refer.

PART I – ADMINISTRATIVE DATA AND PRODUCT INFORMATION

SECTION A: PRODUCT PARTICULARS

Details of the following as entered under Step 1 will appear automatically in the application form:

1. Product name;
2. Name and Strength of Active Ingredients
Name and Strength of Excipients; and
3. Dosage form.

Other fields as follow, shall be completed:

4. Product Description:

State, briefly on **visual and physical characteristics** of the product, including (where applicable):

- Shape, size, superficial markings for identification purposes, colour, odour, taste, consistency, type of tablet coating, type of capsule, etc.

- When describing liquids, state clearly whether it is in the form of a solution (clear), suspension, emulsion, etc.

5. Pharmacodynamics (for full evaluation only)

Please provide a concise and comprehensive summary of the pharmacological profile:

- Main and supplementary pharmacological effects (mechanism of action, actions other than the therapeutic effects);
- Relevant pharmacokinetics (absorption, plasma-protein binding, distribution, biotransformation, metabolism, excretion, etc);
- Bioavailability and bioequivalence studies in man.

6. Pharmacokinetics (for full evaluation only)

- Details are as for A5.1 Pharmacodynamics stated above.

7. Indication

- State briefly on the recommended clinical use(s) of product, indicating clearly whether curative, palliative, adjunctive, diagnostic, etc.
- Indications should be specific; phrases such as ‘associated conditions’ or ‘allied diseases’ would not normally be considered appropriate.
- Indications other than those specified and accepted at the time of registration must not be included in any product literature, data sheets, package inserts, labels, etc. without prior permission of the Authority.
- Should it be desired to include new indications, an application shall be filed to the Authority together with supporting clinical documentation on evidence of efficacy and safety for the additional uses (indications).
- In the case of products which are to be used as health supplements, no claims shall be made for the prevention and treatment of disease states.
- For natural products, please state briefly on recommended use(s) of the product, starting with the phrase “Traditionally used for...../ Homeopathically used for.....”.

8. Recommended Dose OR Dose/ Use Instruction

Recommended Dose (for full evaluation only):

- Please state the dose (normal dose, dose range) and dosage schedule (frequency, duration); and route of administration appropriate for each therapeutic indication.
- Dosage for adults, and, children (where appropriate) shall be stated.
- Dosage adjustments for special conditions, e.g. renal, hepatic, cardiac, nutritional insufficiencies (where relevant) shall be stated.
- Where appropriate, diluents and instructions for dilution, reconstitution and use or administration of the product shall be clearly stated.
- Distinction shall be made between therapeutic and prophylactic doses, and between dosages for different clinical uses, where applicable.
- Ensure that dosage recommendation is relevant and appropriate for the product.

Dose/ Use Instruction (for abridged evaluation only):

- State the dose (normal dose, dose range) and dosage schedule (frequency, duration) [and route of administration appropriate for each therapeutic indication]. Dosage for adults, and where appropriate children, should be stated.
- Dosage adjustments for special conditions e.g. renal, hepatic, cardiac, nutritional insufficiencies, where relevant, shall be stated.

9. Route of Administration (for full evaluation only)

- Details are as for Recommended Dose stated above.
- Please select route of administration from the drop-down list, e.g. intramuscular, oral, rectal, sublingual, etc.

10. Contraindication

- Please state conditions for which or under which the product shall not be used.
- Indicate clearly which conditions are :

- absolutely contraindicated;
 - contraindicated but may be used under special circumstances and what precautions to be taken in such cases.
-
- Where there is likelihood that additives are added, especially for intravenous solutions, foreseeable contraindicated additives shall be mentioned (where applicable).
 - Concurrent drug therapy which are contraindicated shall also be included where possible (where applicable).

11. Warnings and Precautions

- Please state briefly on warnings and precautions, where necessary to ensure safe use; and efficacious (where applicable) of the product; (e.g. caution against giving to children and elderly; against driving motor vehicles or manning heavy machinery after intake of product; use in pregnancy and lactation; in infants; etc.)

12. Interactions With Other Medicaments

- Please state interactions which are observed and/or for which there is potential clinical significance.
- Interactions may occur with:
 - medicinal products used for the same indication;
 - medicinal products used for other indications;
 - meals, or specific types of food.

13. Pregnancy and Lactation

Use in Pregnancy:

- The following shall be stated:
 - a) conclusions from the animal reproduction/ fertility study and the human experience;
 - b) the risk in humans at different stages of pregnancy, as assessed from a);
 - c) information on the possibility of using the medical product in fertile and pregnant women.

Use in Lactation:

- When the active substance(s) or its metabolites are excreted in milk, recommendations as to whether to stop or continue breast feeding, and the likelihood and degree of adverse reaction in infant shall be stated.

For abridged evaluation, please state any effect on pregnancy and lactation, if applicable.

14. Side Effects/ Adverse Reactions

- Please state in order for severity and frequency, the side effects, adverse reactions, toxic effects, etc. (i.e. reactions, toxic effects, other than those desired therapeutically) including reactions such as allergy, hypersensitivity, drug dependence, addiction, carcinogenicity, tolerance, liver/ kidney toxicity etc.
- Indicate also symptoms and sites of effects/ reactions.
- Reactions, whether minor or serious shall be stated.
- Severity, reversible, frequency of occurrence shall be indicated, wherever possible.
- Clinical tests for detection of 'sensitive' patients, measure for management of adverse reactions developed shall be described wherever possible.

15. Signs and Symptoms of Overdose and Treatment

- Please state briefly symptoms of overdose/ poisoning, and where possible, recommended treatment and antidotes for overdose/ poisoning.

16. Storage Conditions

- Please state the recommended storage conditions (temperature, humidity, light etc.).
- Information include storage condition before first opening, after reconstitution and/or after opening and for all the listed pack types shall also be provided, where applicable. Stability data to support such storage condition shall be submitted.

17. **Shelf Life**

- Shelf life for all the listed pack types shall be supported by stability data.
- Information include shelf life before first opening, after reconstitution and/or after opening where applicable shall also be provided. Stability data to support such shelf life shall be submitted.
- Evidence is required to demonstrate that the product is stable which meets the finished product shelf life specifications throughout its proposed shelf-life and toxic decomposition products are not produced in significant amounts during this period; potency, sterility and efficacy of preservative, etc. are maintained.

18. **Therapeutic Code**

- Please indicate WHO assigned ATC code for each distinct therapeutic indication proposed for a product, if such a code is available. Click button 'click here to search' to search the code via database at <http://www.whooc.no/atcddd/>.
- For natural products, please select "Traditional/ Homeopathy" from the listed button.

After completion of Section A has been done, please click Section List for display of main page of application form and select Section B: Product Formula, or click button 'next' after saving the entered data.

SECTION B: PRODUCT FORMULA

- a) For full evaluation requirement, B1.1 and B1.2 as described below is required under Section B: Product Formula. Data pertaining to quality of product is required to be submitted under Part II: Quality of Product.

B1.1 Batch Manufacturing Formula

- Please state batch size and actual batch manufacturing master formula.

- Data from validation step will be captured in terms of substance name, type (active or excipient ingredient), function and quantity per unit dose.
- Other information such as overage (where applicable) shall be entered.

B1.2 Attachment of the Batch Manufacturing Formula Documentation

- The attachment shall be submitted.

b) For abridged evaluation requirement, Batch Manufacturing Formula is required under B1.1 and Attachment of the Batch Manufacturing Formula documentation is required under B4 of the same section i.e. Section B.

Whereas B2.1, B3, B4 and B5 appear as below:

B2.1 Manufacturing process

- Please state a brief description of the manufacturing process.
- Essential points of each stage of manufacturing process and a description of the assembling of the product into final containers shall be covered. If the product is repacked/ assembled by another manufacturer, details of repacking/assembly and quality control shall be supplied.
- An **attachment** of the manufacturing process, in the form of a flow chart can be submitted under B2.2.

B3. In-Process Quality Control

- Please attach document for In-Process Quality Control to provide a summary of the tests performed, stages at which they are done, and the frequency of sampling and number of samples taken each time.
- Specifications for quality assurance of the product shall be supplied.

B4. Attachment of Finished Product Specification Documentation

- Please attach document for Finished Product Specification to provide details of quality control specifications, including a list of tests for both release and shelf life specifications (if they are different); and state the limits of acceptance.

B5. Attachment of Stability Data Documentation

- Reports of stability studies shall provide details of :
 - the batches placed under study (a minimum of 2 batches are required);
 - containers/ packaging type;
 - conditions of storage during study (temperature, humidity, etc);
 - duration of study and frequency (interval) of the tests/ observations;
 - the tests performed (including degradation products being monitored) and acceptance limits.

SECTION C: PARTICULARS OF PACKING

- This section is subjected to requirements as stated in [Appendix 10](#): Guide for Implementation of Patient Dispensing Pack for Pharmaceutical Products in Malaysia. Please refer the appendix for details.
- Please enter particulars of packing in the following sub-sections:

C1 : Pack Size

- Please select pack size by weight or volume or quantity; and unit

C2 : Immediate Container Type

- Please select container type, e.g. aluminium, glass, metal, paper, plastic, others (if others, please specify)
- Please enter description of container type
- Please attach attachment of container type at table appeared after 'Add' button at the bottom page is clicked

C3 : Barcode/ Serial No.

- Please key in if any (optional)

C4 : Recommended Distributor's Price

- Please key in if any (optional)

C5 : Recommended Retail Price

- Please key in if any (optional)

and then click button 'Add' to save all the entered informations.

Note:

To add next particulars, repeat the same process until all packings are listed accordingly. To remove any item from the listing, select item from the listing and click the "Remove" button.

SECTION D: LABEL (MOCKUP) FOR IMMEDIATE CONTAINER, OUTER CARTON AND PROPOSED PACKAGE INSERT

- This section is subjected to requirements as stated in [Appendix 9: Labelling Requirements](#) and other appendices (where applicable). Please refer the appendices for details.
- Please attached label (mock-up) i.e. draft of the actual product label and proposed package insert at the following sub-sections:

D1. Label (Mock-up) for Immediate Container

D2. Label (Mock-up) for Outer Carton (Unit Carton)

D3. Proposed Package Insert

SECTION E/ SECTION F: SUPPLEMENTARY DOCUMENTATION (AND PARTICULARS OF PRODUCT OWNER, MANUFACTURER, IMPORTER AND OTHER MANUFACTURER)

a) Product Owner

Please select one of the following for status of product owner:

- Manufacturer or
- Product registration holder or
- Product registration holder & manufacturer or
- Others (If the product owner is neither of the above status) – Please enter name and address of the product owner.

b) Letter of Authorization from Product Owner

- All applications for registration shall be accompanied with Letter of Authorization from product owner.
(Not applicable if the Product Registration Holder is Product Owner).
- Letters of Authorization (LOA) shall be valid and current at the time of submission.
- The LOA shall be on the product owner's original letterhead and be dated and signed by the Managing Director, President, CEO or an equivalent person who has overall responsibility for the company or organization.
- The LOA shall state the name of the product concerned and also the name and actual plant address of the manufacturer(s) involved in the manufacture of the product.

c) Letter of Appointment of Contract Manufacturer from Product Owner

- Please attach (if applicable).
- Applicable for product which is contract manufactured by a manufacturer who is not the product owner.

d) Letter of Acceptance from Contract Manufacturer

- Please attach (if applicable).
- The letter of acceptance from the manufacturer shall be on the manufacturer's original letterhead and be dated and signed by the Managing Director, President, CEO or an equivalent person who has overall responsibility for the company or organization.
- The letter of acceptance shall state the name of the product concerned and also the name and actual plant address of the manufacturer(s) involved in the manufacture of the product.

e) Is the active ingredients patented in Malaysia?

- Click the appropriate button 'Yes' or 'No'.

- If yes, please attach the related document.
- Applicants who hold valid patents shall provide documentary evidence of the nature and extent of their patents.

f) Certificate of Pharmaceutical Product (CPP), Certificate of Free Sale (CFS) and Certificate of Good Manufacturing Practice (GMP)

- Please attach the certificates.
- Please key in issuing body, date of issue, date of expiry of the certificates. If the issuing body is not listed, please select 'Not Listed' button. Automatic email will be sent to NPCB for verification.
- The certificates shall be valid and current at the time of submission.
- For imported products, the following requirements shall be furnished, either a:
 - i) CPP from the competent authority in the country of origin; OR
(Note: In the event a CPP is not available from the country manufacture, e.g. where a product is not licensed for sale in said country because its manufacturer is manufacturing under contract only for product owner from another country, the following alternatives may be considered: GMP Certification/ Manufacturing License for the manufacturer from the relevant competent authority, together with CPP from the country of the product owner; or CPP from country of release, if CPP from the country of the product owner is not available)
 - ii) CFS and GMP from the relevant competent authorities is deemed acceptable by the Authority for health supplements and natural products only.
- CPP shall be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce & be issued by the Health Authorities listed in the WHO Certification Scheme (*list is available from WHO website: <http://www.who.int>*).
- CPP which is issued by EMA for products registered through the centralized procedure in EU will be accepted.
- CPP issued by the manufacturer or other authorities are not acceptable.
- If more than one manufacturer is involved in the manufacture of a product, GMP certification shall be available for all the manufacturers.

- The Authority reserves the right to conduct an inspection on any manufacturing site.
- Unless otherwise supported by justifications acceptable to the Authority, the following products are unlikely to be registered:
 - i) products not licensed/ certified for sale in the country of manufacture/ product owner;
 - ii) products manufactured for export only (imported products).

g) Is this product licensed to be placed on the market for use in the exporting country?

If no, please state the reason.

h) Is the product on the market in the exporting country?

If no, please state the reason.

i) Summary of Product Characteristics (SPC)

Please attach (where applicable).

j) Patient Information Leaflet (PIL)

Please attach (where applicable).

k) Attachment of Protocol Analysis, Analytical Validation

Please attach (where applicable).

l) Certificate of Analysis (CoA) for Finished Product

- For two (2) batches.
- Compulsory for imported product.
- Please attach the certificate (which must be complete with the product specification and results).

m) Importer and Store Address

Please key in (where applicable).

n) Other Supporting Document

Please attach (if any).

PART II, III & IV – QUALITY , NONCLINICAL DOCUMENT & CLINICAL DOCUMENT

In order to complete these parts, please refer the main DRGD as well as ASEAN Common Technical Requirements Guidance Documents, and the following documents (where applicable):

- a) Appendix 2: Requirements for Product Registration
- b) Appendix 3: Guidelines on Registration of Biologics
- c) Appendix 4: Guideline on Registration of Health Supplements
- d) Appendix 5: Guideline on Registration of Natural Products
- e) Appendix 6: Guideline on Regulatory Control of Active Pharmaceutical Ingredients (API)

APPENDIX 12

CONDITIONS AND SUPPORTING DOCUMENTS REQUIRED FOR AN APPLICATION OF VARIATION

a) VARIATION TYPE I (MINOR VARIATION)

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
1.	Change in name of manufacturer and/or other manufacturers without any change in address of site.	<ul style="list-style-type: none"> • E13 (manufacturer) • E14 (other manufacturers) • D1 • D2 • D3 • E6 • E12 	<ul style="list-style-type: none"> • E2 (manufacturer) • E3 (other manufacturers) • D1 • D2 • D3 • F6 • F12 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. The manufacturing/ other manufacturing site of the drug product remains unchanged. 2. No other changes to the label/ package insert except for the change of the name of a manufacturer/ other manufacturers of the drug product. 3. The manufacturing site remains the same. <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. For local manufacturers/ other manufacturers: Certificate of name change i.e. Form 13 Company Act 1965. (Please attach the supporting document at E12/ F12). 2. For foreign manufacturers/ other manufacturers: A valid Good Manufacturing Practice (GMP)

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				<p>certificate.</p> <p>3. Official letter from product owner authorizing the manufacturer with new name to manufacture the drug product.</p> <p>4. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).</p>
2.	Replacement, addition or deletion of company logo on the packaging components (without any changes on graphic or label content)	<ul style="list-style-type: none"> • D1 • D2 • D3 	<ul style="list-style-type: none"> • D1 • D2 • D3 	<p><u>SUPPORTING DOCUMENT</u></p> <p>Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).</p>

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
3.	Change in product owner	<ul style="list-style-type: none"> • E1.1 • E1.2 • E2.1 • E2.2 • E12 • D1 • D2 • D3 (if applicable) 	<ul style="list-style-type: none"> • E1 • F1 • F2.1 • F2.2 • F12 • D1 • D2 • D3 (if applicable) 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. The Product Registration Holder remains the same. Submission shall be done by current PRH. 2. The manufacturing site remains the same. <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Letter of confirmation for change in product ownership countersigned by both old and new product owner. 2. Official letter from the new product owner declaring the change, and authorizing the local license holder to be responsible for the product license. 3. In the case of a contract manufacturer, new product owner to issue Letter Of Appointment to contract manufacturer and contract manufacturer to issue Letter Of Acceptance. 4. Revised labels and package insert (if applicable).
4.	Change in importer/ store address.	<ul style="list-style-type: none"> • E13.1 (importer) • E15 (store address) 	<ul style="list-style-type: none"> • E2.1 (importer) • E4 (store address) 	

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
5.	Change or addition of imprints, bossing or other markings (except scoring/break lines) on tablets or printing on capsules, including replacement, or addition of inks used for product marking.	<ul style="list-style-type: none"> • A4 • P1 • P5.1 • P5.2 • D3 • E8 (if applicable) • E9 	<ul style="list-style-type: none"> • A2 • D3 • F8 (if applicable) • B4 • F9 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. Any new ink must be of oral pharmaceutical/ food grade and not a listed banned substance. 2. Release and end-of-shelf life specifications of the drug product remain unchanged except for appearance. 3. New markings do not cause confusion with other registered products. <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Release and end-of-shelf life specifications of the drug product with the new product description. 3. Certificate of analysis (CoA) of new ink. 4. Details of the proposed new inks (where applicable) 5. Detailed drawing or written description of the current and proposed imprint/ bossing/ markings.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
6.	Change in shape or dimensions of the container or closure without any other changes.	<ul style="list-style-type: none"> • P7 • C (if applicable) 	<ul style="list-style-type: none"> • C (if applicable) 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. The primary packaging material of container or closure remains the same. 2. Not applicable for sterile products. 3. No change is made to the product shelf life and/or storage conditions. 4. No change in the qualitative or quantitative composition of the container and/or closure and the change do not affect the delivery, use, safety or stability of the drug product. <p><u>SUPPORTING DOCUMENTS</u></p> <p>Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).</p>
7.	<ul style="list-style-type: none"> • Change in pack size of the drug product (Finished product), without change in primary packaging material. • Change in the number or units (e.g. tablets, ampoules) in a pack. 	<ul style="list-style-type: none"> • C • D1 • D2 • D3 • E8 (if applicable) • P7 	<ul style="list-style-type: none"> • C • D1 • D2 • D3 • F8 (if applicable) 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. The primary packaging material of container or closure remains the same. Primary packaging material is the material that is in contact with the finished product and may affect the delivery, use, safety or stability. 2. No other changes to the label/ package insert except for the pack size. 3. The new size is consistent with the dosage regimen and duration of use as approved in the

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
	<ul style="list-style-type: none"> Change in volume of non sterile preparations 			<p>package insert.</p> <p><u>SUPPORTING DOCUMENTS</u></p> <p>Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).</p>
8.	Tightening of specification limits of drug product (finished product) and/or drug substance (active ingredient)	<ul style="list-style-type: none"> E9 E10 E11 P5.1 P5.2 P5.4 S4.1 S4.2 S 4.4 	<ul style="list-style-type: none"> B4 F9 F10 (finished product) F11 (active ingredient) 	<p><u>CONDITION</u></p> <p>1. Any change should be within the range of currently approved limits.</p> <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Tabulation of the current and revised release and shelf life specifications of the drug product/drug substance with changes highlighted. 2. Certificate of Analysis (CoA) for drug product or drug substance. 3. Protocol analysis for drug product/ drug substance. 4. Revised specification of drug substance. 5. Specifications of drug product. 6. Batch analysis of drug product.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
9.	<p>Change in particular of manufacturer of drug substance (active ingredient) without any change in specification</p> <p>a. Change in manufacturer of drug substance</p> <p>b. Addition of manufacturer of drug substance</p> <p>c. Change in name and/or rephrasing of address of a manufacturer of drug substance.</p>	<ul style="list-style-type: none"> • S2.1 • S4.4 	<ul style="list-style-type: none"> • F11 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. Finished product release and end of shelf life specification remains the same. 2. Method of preparation and route of synthesis remain the same. 3. For (c), the manufacturing site of the drug substance remains the same. <p><u>SUPPORTING DOCUMENTS</u></p> <p>For (a) & (b):</p> <ol style="list-style-type: none"> 1. Certificate of Analysis (CoA) for drug substance (Also include CoA from all of the drug substance manufacturers proposed to be retained) or batch analysis of drug substance. 2. Certificate of Suitability (CEP) for the drug substance or Drug Master File; or reference to DMF by USFDA, TGA or JFDA (if applicable). 3. Tabulation of the differences compared with the registered manufacture information (if applicable). <p>For (c):</p> <ol style="list-style-type: none"> 1. Updated information of the manufacturer of the drug substance. 2. Official document/ evidence when required.

NO.	VARIATION TYPE I (MINOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
10.	Change in secondary packaging material (or change in any part of the primary packaging material that is not in contact with the finished product (e.g. colour of flip off caps, colour code rings on ampoules, change of needle shields i.e. different plastic used).	<ul style="list-style-type: none"> • C • D2 • D3 • P7 	<ul style="list-style-type: none"> • C • D2 • D3 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. The primary packaging material of container or closure remains the same. 2. The change does not affect the delivery, use, safety or stability of the finished product <p><u>SUPPORTING DOCUMENT</u></p> <p>Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).</p>
11.	Change in testing procedure of an excipient	<ul style="list-style-type: none"> • P4.2 • P4.3 	Not applicable	<p><u>CONDITION</u></p> <p>Specifications of the excipient and drug product (finished product) remain the same.</p>

b) VARIATION TYPE II (MAJOR VARIATION)

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
1.	Change of product name.	<ul style="list-style-type: none"> • A1 • D1 • D2 • D3 • E4 (if applicable) • E8 (if applicable) 	<ul style="list-style-type: none"> • A1 • D1 • D2 • D3 (if applicable) • F4 (if applicable) • F8 (if applicable) 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. No change to product (formulation, specification etc) except for the product name 2. No confusion with other already registered product's name. 3. The new name does not (1) suggest greater safety or efficacy than supported by clinical data (2) imply a therapeutic use (3) imply superiority over another similar product (4) imply the presence of substance(s) not present in the product. 4. Health Supplements & Natural Products - Please refer Appendix 4 and Appendix 5, respectively. <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 2. Letter confirming change in name only issued by the product owner or PRH. 3. A declaration from the applicant that there is no change to the product/ label except name. 4. Updated CPP if applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
2.	Change in content of leaflet or prescribing information/ PIL/ SPC.	<ul style="list-style-type: none"> • A1 – A17 • D1 • D2 • D3 • E7 • E8 (if applicable) 	<ul style="list-style-type: none"> • A1 – A13 • D1 • D2 • D3 • F7 • F8 • F12 	<p><u>CONDITION</u></p> <p>As a subsequent change due to revision of datasheet approved by regulatory authority e.g. Summary of Product Characteristics (SPC), or US Package Insert (USPI) or equivalent document.</p> <p>For natural products: Proposed indication shall be within those listed under Appendix 5.</p> <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. For all types of product please provide revised drafts of the package insert and labeling incorporating the proposed variation with: <ol style="list-style-type: none"> a. Copy with amendments clearly marked. b. Clean copy of the proposed new package insert. 2. For innovator product please provide: <ol style="list-style-type: none"> a. Datasheet approved by regulatory authority e.g. Summary of Product Characteristics (SPC), or US Package Insert (USPI) or equivalent document. b. Conclusion or abstract of recent Periodic Safety Update Report where applicable. c. Expert Clinical Report (if applicable) d. Company Core Datasheet where applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				<p>3. For generic product please provide supporting documents e.g. Martindale or equivalent document to support the change.</p> <p>4. For natural products, please provide:</p> <p>a) Justification for the proposed change.</p> <p>b) Supporting documents from the clinical papers, Chinese Pharmacopoeia and/or herbal monograph/ compendium on the therapeutic uses and safety aspect of the relevant active ingredient/s.</p>
3.	Change in content of label inclusive of change in graphics/ artwork.	<ul style="list-style-type: none"> • D1 • D2 • D3 	<ul style="list-style-type: none"> • D1 • D2 • D3 	<p><u>CONDITIONS</u></p> <p>For Natural Products Please refer to (List of Prohibited Visuals/ Graphics On Label of Natural Products in Appendix 5)</p> <p><u>SUPPORTING DOCUMENT</u></p> <p>Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).</p>

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
4.	Change in manufacturing process of the finished product	<ul style="list-style-type: none"> • E11 • P3.2 • P3.2.1 • P3.3 • P3.4 • P5.1 • P5.4 • P8 	<ul style="list-style-type: none"> • B2.1 • B2.2 • B3 • B4 • B5 • F10 (CoA of finished product) 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. The same currently approved manufacturing site. 2. The change does not cause a negative impact on the quality, safety and efficacy of the drug product. 3. Finished product specification is not adversely affected. <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Description of the proposed change in manufacturing process. 2. Comparative batch analysis data between the currently approved and proposed manufacturing processes OR Certificate of Analysis (CoA), where applicable. 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Comparative dissolution profile data between the products manufactured in the currently approved and proposed manufacturing process for oral solid dosage forms as per compendium and validation batches, where applicable. 5. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies, where applicable.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				<p>For abridged-products, only supporting documents (1), (2) and (3) are required.</p> <p>Process validation report may be requested when deemed necessary.</p>
5.	Change in overage of active ingredient	<ul style="list-style-type: none"> • B1.2 • E11 • P5.4 • E12 • P8 	<ul style="list-style-type: none"> • B1.2 • F10 • F12 • B5 	<p><u>CONDITION</u></p> <p>Finished product release and end of shelf life specification remains the same.</p> <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Certificate of Analysis (CoA) of drug product. 2. Justification for the change. 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Batch manufacturing formula. 5. Comparative batch analysis data of drug product. 6. Table of comparison of proposed and current batch manufacturing formula. 7. Letter of commitment to undertake the proposed change under real time stability study.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
6.	Replacement of an excipient with a comparable excipient and/or change in content of excipient.	<ul style="list-style-type: none"> • A2.1 • B1.2 • P1 • P4.1 • P4.2 • P3.2 • P3.2.1 • E11 • P5.4 • P8 • E12 • D1 • D2 • D3 (if applicable) 	<ul style="list-style-type: none"> • A4.2 • B1.2 • B2.1 • B2.2 • B3 • B4 • B5 • F10 • F12 • D1 • D2 • D3 (if applicable) 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. Finished product release and end of shelf life specification remains the same. 2. There is no change in dissolution profile for oral solid dosage forms (where applicable). 3. Replacement of an excipient with a comparable excipient of the same functional characteristics. 4. No changes on the specification of the excipient for product specific requirements (e.g. particle size profiles, polymorphic form, etc.), if applicable. 5. Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Comparison of new and existing formula. 2. Batch Manufacturing Formula. 3. Excipient specification (if applicable). 4. Manufacturing process with amendments. 5. Certificate of Analysis (CoA) of drug product. 6. Justification for not submitting a new bioequivalence study according to ASEAN Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (where applicable). 7. Comparative dissolution profile data of at least one representative pilot/production batch of the drug product between the currently approved and

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				<p>proposed solid dosage forms formulation (where applicable).</p> <p>8. Stability data of drug product (please refer to ASEAN Guideline On Stability Study of Drug Product)</p> <p>9. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).</p> <p>10. Batch analysis data.</p> <p>11. Product interchangeability/ equivalent evidence (if any).</p> <p>12. Justification for the change supported by appropriate development of pharmaceuticals.</p> <p>13. New unit formula for coating agent (where applicable).</p>
7.	Change in batch size	<ul style="list-style-type: none"> • B1.2 • E11 • P5.4 • P3.4 • E12 • P3.2 • P3.2.1 (if applicable) 	<ul style="list-style-type: none"> • B1.2 • F10 • F12 • B2.1 • B2.2 (if applicable) 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. The change does not affect the reproducibility and/or consistency of the product. 2. No change to the manufacturing method nor to the in-process controls other than those necessitated by the change in batch-size, e.g. use of different size equipment. 3. Finished product release and end of shelf life specification remains the same. <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Comparative tabulated format of the proposed and

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				current manufacturing formula. 2. New batch manufacturing formula. 3. Batch analysis data (in a comparative table). 4. Certificate of analysis for 2 batches of drug product. 5. Process validation report (may be requested when deemed necessary). 6. Justification for the change. 7. Letter of commitment to undertake the proposed batch size under real time stability studies. 8. Description of the manufacturing process (if applicable).
8.	Change in hard capsule shell (colour, size or source)	<ul style="list-style-type: none"> • A4 • P1 • P8 • E11 • P4.5 • P5.4 • E12 • P5.1 • E9 • D1 • D2 • D3 (if applicable) 	<ul style="list-style-type: none"> • A2 • A3.2 • B4 • B5 • F9 • F10 • D1 • D2 • D3 (if applicable) 	<u>CONDITIONS</u> <ol style="list-style-type: none"> 1. Includes change of hard gelatin capsule to vegetable capsule but does not apply change from hard gelatin capsule to soft gel capsule. 2. Any new coloring agent used must be of oral pharmaceutical/ food grade and not a listed banned substance. 3. Same functional characteristics, no change in dissolution profile for solid dosage forms 4. Finished product release and shelf life specifications remain the same except for the product description. <u>SUPPORTING DOCUMENTS</u> <ol style="list-style-type: none"> 1. Stability data of drug product (please refer to

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				<p>ASEAN Guideline on Stability Study of Drug Product) where applicable.</p> <ol style="list-style-type: none"> 2. Certificate of analysis (CoA) of drug product with the new description. 3. For empty hard capsule made of ruminants source, Transmitting Animal Spongiform Encephalopathy (TSE)-free certificate issued from relevant veterinary authority of the issuing country- 4. Certificate of analysis of the new capsule shell. 5. Revised specifications of drug product. 6. Batch analysis data. 7. Comparative dissolution profile data of drug product. 8. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
9.	Change in finished product or active ingredient specification (includes addition of a new test parameter)	<ul style="list-style-type: none"> • E9 • E10 • E11 • P5.1 • P5.4 • P5.6 • S4.1 • S4.2 • S4.3 • S4.4 	<ul style="list-style-type: none"> • B4 • F9 • F10 • F11 	<p><u>CONDITIONS</u></p> <p>The change should not be the result of unexpected events arising during manufacture or because of stability concerns.</p> <p><u>SUPPORTING DOCUMENTS</u></p> <p>1. For change in finished product specifications:</p> <ul style="list-style-type: none"> a. Certificate of analysis of drug product as per the new specifications: b. Comparative table of approved and proposed specifications with justification c. Appropriate analytical validation data d. Revised specifications of drug product. e. Revised analytical procedures. f. Batch analysis data of drug product. <p>2. For change in active ingredient/ drug substance specifications:</p> <ul style="list-style-type: none"> a. Comparative table of approved and proposed specifications with justification b. Specification of drug substance, c. Analytical procedures of drug substance, d. Validation of analytical procedures, e. Batch analysis of drug substance

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
10.	Change to in-process tests or limits applied during manufacture of the product.	<ul style="list-style-type: none"> • P3.3 • P3.4 • E9 • E10 	<ul style="list-style-type: none"> • B3 • F9 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. Includes tightening of in-process limits and addition of new tests 2. Release and shelf-life specifications of drug product remain unchanged <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable). 2. Revised in-process specifications together with justification and relevant process validation data.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
11.	Change or addition in primary packaging material	<ul style="list-style-type: none"> • C • D1 • D2 • D3 • P3.2 • P3.2.1 • P7 • P8 • E8 (if applicable), • E12 	<ul style="list-style-type: none"> • C • D1 • D2 • D3 (if applicable), • B5, • F8 (if applicable) • F12 	<p><u>CONDITIONS</u></p> <p>Release and shelf life specification remains the same.</p> <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Assembly process for the new packaging material/ revised manufacturing process and revised flow chart (if any) 2. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 3. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 4. Justification for the change in packaging material and appropriate scientific studies on the new packaging. 5. For semisolid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs. (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack). 6. Container closure system (if applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
12.	Change in shelf life of finished product:- a) As packaged for sale b) After first opening c) After dilution/ reconstitution	<ul style="list-style-type: none"> • A16 • P8 • E12 • D1 • D2 • D3 	<ul style="list-style-type: none"> • A13 • B5 • F12 • D1 • D2 • D3 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. For (a) & (b) - The studies must show conformance to the current shelf life specification. 2. For (c) - Studies must show conformance to the current shelf life specification for the reconstituted product. <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Results of appropriate real time stability studies covering the duration of proposed shelf-life of at least 2 pilot/ production scale batches of the product in the authorized packaging material <ul style="list-style-type: none"> • as a package for sale and/or • after first opening and/or • after the dilution/ reconstitution <p>In accordance with the ASEAN Guidelines on Stability Study of Drug Product; results of appropriate microbiological testing should be included (where appropriate).</p> <ol style="list-style-type: none"> 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Justification letter for the change of shelf life of the drug product (if applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
13.	Change in storage conditions	<ul style="list-style-type: none"> • A15 • P8 • D1 • D2 • D3 	<ul style="list-style-type: none"> • A12 • B5 • D1 • D2 • D3 	<p><u>CONDITION</u></p> <p>The studies must show conformance to the current shelf life specification.</p> <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Results of appropriate real time stability studies covering the duration of currently approved end-of-shelf life (at proposed storage condition) of at least 2 pilot/ production scale batches of the product and in the authorized packaging material in accordance with the ASEAN Guidelines on Stability Study of Drug Product. 2. Revised drafts of the package insert and labeling incorporating the proposed variation (if applicable).
14.	Appointment, deletion or change of other manufacturers	<ul style="list-style-type: none"> • D1 • D2 • D3 • E14 • E12 	<ul style="list-style-type: none"> • E3 • F12 • D1 • D2 • D3 	<p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. GMP certificates of the proposed other manufacturers. 2. Description of the manufacturing activity of all other manufacturers involved (including assembling process). 3. Letter of appointment and acceptance for contract of other manufacturers. 4. Revised drafts of the labeling incorporating the proposed variation (where applicable).

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
15.	Addition or deletion of scoring/ break line on tablet	<ul style="list-style-type: none"> • A4 • P1 • D1 • D2 (if applicable) • D3 • E9 • E11 • P5.1 • P5.4 • E12 	<ul style="list-style-type: none"> • A2 • B4 • F9 • F10 • F12 • D1 • D2 • D3 (if applicable) 	<p><u>CONDITIONS</u></p> <p>Finished product release and shelf life specifications remain the same except for the product description.</p> <p><u>SUPPORTING DOCUMENTS</u></p> <ol style="list-style-type: none"> 1. Certificate of analysis (CoA) FPQC X 1 batch (shall include data on the test of uniformity of content of the subdivided parts of tablets at release). 2. Revised drafts of the package insert and labeling incorporating the proposed variation (where applicable). 3. Release and end-of-shelf life specifications of the drug product with the new product description.
16.	Change in test procedure or analytical protocols of finished product.	<ul style="list-style-type: none"> • E9 • E10 • E11 • P5.4 	<ul style="list-style-type: none"> • B4 • F9 • F10 	<p><u>CONDITIONS</u></p> <ol style="list-style-type: none"> 1. Finished product specifications are not adversely affected. 2. Appropriate analytical validation or re-validation studies have been performed in accordance with relevant guidelines. 3. Results of method validation show new test procedure to be at least equivalent to the former procedure.

NO.	VARIATION TYPE II (MAJOR VARIATION)	AFFECTED FIELDS		SUPPORTING DOCUMENTS REQUIRED AND CONDITIONS APPLIED
		FULL EVALUATION	ABRIDGED EVALUATION	
				<u>SUPPORTING DOCUMENTS</u> <ol style="list-style-type: none"> 1. Appropriate verification/ validation data and comparative analytical results between the currently approved and proposed test. 2. Revised protocol of analysis. 3. Certificate of analysis of drug product.
17.	Change or addition of fill volume and/or change of shape or dimension of container or closure for a sterile solid and liquid drug product	<ul style="list-style-type: none"> • P3.4 • P8 • E12 • C • D1 • D2 • D3 (if applicable) 	Not applicable	<u>CONDITIONS</u> <ol style="list-style-type: none"> 1. Release and end-of-shelf life specifications of the drug product are not affected. 2. The packaging material remains the same. <u>SUPPORTING DOCUMENTS</u> <ol style="list-style-type: none"> 1. Justification that the proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert. 2. Validation data of the manufacturing process, sterilization and container closure system (if applicable). 3. Stability data of drug product (please refer to ASEAN Guideline on Stability Study of Drug Product) where applicable. 4. Revised drafts of the package insert and labeling incorporating the proposed variation, where applicable.

APPENDIX 13:**SUPPORTING DOCUMENTS REQUIRED FOR CHANGE OF MANUFACTURING SITE (COS) APPLICATION**

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
1.	Letter of authorization/ appointment from the product owner to authorize Product Registration Holder to submit the change of site application. In case of a contract manufacturer, a letter of acceptance from the proposed contract manufacturer to manufacture the product.	√	√	√	√	√
2.	Letter from the manufacturer/ product owner to clarify/ explain the need to change site of manufacture. <u>For Type I:</u> Letter of declaration stating the reason(s) for change of manufacturing site and clearly state the proposed and current name and address of manufacturer	√	√	√	√	√
3.	Written declaration from the manufacturer to certify that the manufacturing process, and the release and expiry (check) specifications of the product as the same as already approved. <i>OR</i> If there are minor changes, to declare the 'minor changes' & justify the need for such changes.	√	√	√	√	√
4.	'Release' and 'end-of-shelf life' specifications from proposed site.	√	√	√	√	√
5.	Original copy of the Certificate of Free Sale (CFS) and Good Manufacturing Practice (GMP)/ Certificate of Pharmaceutical Product (CPP) from the source country of the new manufacturing site in the case of an imported product <i>OR</i> Letter of confirmation on GMP status or valid manufacturer's license for the new manufacturing site.	√	√	√	√	√

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
6.	Original copy of Certificate of Analysis (CoA) from the new manufacturing site.		√	√	√	
7.	<p>“Accelerated” and on-going stability data as per ASEAN Guideline on Stability Study of Drug Product and a letter of commitment to submit real time stability data.</p> <p><u>For Type I:</u></p> <p>Letter of commitment to submit stability data report.</p>	√	√	√	√	
8.	Amended immediate label, outer label and package insert for the product from the proposed site.	√	√	√	√	√
9.	<p>Process validation report as per ASEAN Guideline On Submission Of Manufacturing Process Validation Data For Drug Registration.</p> <p><u>For Type I:</u></p> <p>Letter of commitment to submit process validation report, if applicable</p>	√	√	√	√	
10.	Declaration and commitment that the manufacturer will carry out continuous quality monitoring on the post change products	√				
11.	Letter of commitment to submit stability data, certificate of analysis, process validation report (where applicable) and sample for laboratory testing within 6 months of approval of site change.					√
12.	A written plan for assessing the effect of the change of site on the quality of the product with the objective of demonstrating that the pre- and post-change products are equivalent.	√	√		√	

No	Document To Be Submitted	Type I	Type II	Type III	Type IV	Type V
13.	<p>Comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for “biowaiver”.</p> <p><i>For further information, please refer circular:</i> Bil (31) dlm. BPFK/PPP/01/03</p> <p>OR</p> <p>Report of bioavailability and bioequivalence studies for generic products.</p> <p>OR</p> <p>Comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable.</p> <p><i>(Please refer to ASEAN Guidelines and list of products requiring BA and BE study).</i></p>		√	√		
14.	<p>Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms that are entitled for “biowaiver”.</p> <p><i>For further information, please refer circular:</i> Bil (31) dlm. BPFK/PPP/01/03</p> <p>OR</p> <p>Letter of commitment to submit report of bioavailability and bioequivalence studies for generic products.</p> <p>OR</p> <p>Letter of commitment to submit comparative dissolution profile between the proposed and current site for oral solid dosage forms for innovator products, if applicable.</p> <p><i>(Please Refer to ASEAN Guidelines and list of products requiring BA and BE study).</i></p>	√				√

LIST OF UPDATES

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
1.	January 2013	Section A, 7. Use of <i>Halal</i> Logo	<p>Addition of the following:</p> <p>a) Reference: Circular (95)dIm.BPFIK/PPP/01/03 Jld. 2 at a) Generics (non-scheduled poison), excluding parenteral dosage form and veterinary products.</p> <p>b) As last paragraph: Applicant shall submit application for variation type II to NPCB for approval to affix <i>halal</i> logo on product label of a registered product of which a <i>halal</i> certification has been granted. A copy of the <i>halal</i> certificate must be submitted as a supporting document.</p>	<p>Circular (95)dIm.BPFIK/PPP/01/03 Jld. 2, 26 December 2012: <i>Penggunaan Logo Halal Bagi Produk Farmaseutikal terdaftar kategori produk bukan racun, OTC</i></p>
2.	January 2013	Section A, 1.3.2 Classification of FDI Products	<p>Addition of the following:</p> <p><u>Notes:</u> Applicant shall verify on FDI product classification with NPCB in order to determine whether the product shall be registered by the Authority or otherwise. <i>Reference:</i> Circular (97)dIm.BPFIK/PPP/01/03 Jld. 2</p>	<p>Circular (97)dIm.BPFIK/PPP/01/03 Jld. 2, 27 December 2012: <i>Pengelasan Produk Food-Drug Interface</i></p>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
3.	January 2013	Section E, 14. Maintenance of Registration	<p><u>At 14. Maintenance of Registration:</u></p> <p>Addition of the following paragraph:</p> <p>In order to maintain registration of an imported product, starting on 1st January 2014, applicant shall comply with GMP requirement as stated in the directive issued by the Director of Pharmaceutical Services under Regulation 29, CDCR 1984 <i>Arahan Bil. 1 Tahun 2012 Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB)</i> (Reference: Circulars Bil (25) dlm BPFK/PPP/01/03 Jld 1 and Bil (96)dlm.BPFK/PPP/01/03 Jld. 2). The Authority shall not consider any renewal application that fails to comply with the stipulated requirement.</p> <p>At 16.2.2 Conditions on Good Manufacturing Practice (GMP): Addition of a hyperlink of Bil (96)dlm.BPFK/PPP/01/03 Jld. 2, 28 December 2012: <i>Surat Pekeliling Bagi Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB)</i></p>	<p>Directive Bil (25) dlm BPFK/PPP/01/03 Jld 1, 9 February 2012: <i>Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB)</i> and Circular (96)dlm.BPFK/PPP/01/03 Jld. 2, 28 December 2012: <i>Surat Pekeliling Bagi Direktif Mengenai Syarat Pendaftaran Produk Farmaseutikal Dari Luar Negara Berkaitan Keperluan Amalan Perkilangan Baik (APB)</i></p>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
4.	January 2013	Section A, 1.3.2 Classification of FDI Products	Addition of examples and a hyperlink of the related circular for gamat (Stichopus spp.) at a) <u>Main Criteria</u> , number ii) Substances or ingredients used for therapeutic purposes shall not be added to food. For examples: gypsum fibrosum, pearl powder and gamat (stichopus spp.) .	Circular (98)dIm.BPFK/PPP/01/03 Jld. 2, 8 January 2013: <i>Keperluan Pendaftaran Produk Food-Drug Interface yang mengandungi bahan aktif gamat (Stichopus spp)</i>
5.	January 2013	Section D, 13.2 License Application Form	Addition of a hyperlink at number 4, Import License, regarding requirement of Certificate of Analysis (CoA) for each batch of registered product which is imported into Malaysia.	Circular (99)dIm.BPFK/PPP/01/03 Jld. 2, 11 January 2013: <i>Sijil Analisa (Certificate of Analysis, COA) Untuk Setiap Kelompok Produk Berdaftar Yang Diimport Ke Malaysia</i>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
6.	January 2013	Appendix 5, Guideline on Registration of Natural Products	<ul style="list-style-type: none"> - Amendment at 2.1.3 Prohibited/ Banned Ingredients: <ul style="list-style-type: none"> a) Table 1: Botanicals (and botanical ingredients) containing scheduled poisons as listed under the Poisons Act 1952, for ingredient “Valerian”, as follows: Species: Deletion of “Extract only” Constituent(s) of concern: Addition of “Valepotriates”. b) Table 4: List B: Botanicals which may be Adulterated with Aristolochic Acid: Addition of botanical name starting at Cocculus orbiculatus DC. [Common or Other Names: Moku-boui (Japanese)] to the last botanical names Stephania tetrandra S. Moore and Vladimiria souliei (franch.) Ling - Amendment at 2.7.1 Statement to be stated on product label: “If symptoms persist, please consult a doctor.” and “This is a natural medicine/ <i>Ini adalah ubat tradisional.</i>” OR “This is a homeopathy medicine/ <i>Ini adalah ubat homeopati.</i>” TO <ul style="list-style-type: none"> • For product with an indication “For general health/ well being” or “<i>Untuk kesihatan umum</i>”, please state: <ul style="list-style-type: none"> - “Please consult your pharmacist / doctor before taking 	Memo from Sub-Section of Complementary Medicine (53)dIm.BPFK/PPP/06/17 Jilid 29, 18 January 2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<p>this product or <i>Sila merujuk kepada ahli farmasi/ doktor sebelum mengambil produk ini.</i></p> <ul style="list-style-type: none"> For product with an indication “To relieve symptoms for.... (any illness)” or “<i>untuk mengurangkan tanda-tanda/ simptom....</i>”, please state: <ul style="list-style-type: none"> “Please consult your pharmacist/ doctor if symptoms persist/ worsen or <i>Sila merujuk kepada ahli farmasi/ doktor jika simptom berlarutan/ bertambah teruk.</i>” “This is a traditional medicine/<i>Ini adalah ubat tradisional.</i>” OR “This is a homeopathy medicine/<i>Ini adalah ubat homeopati.</i>” Unless otherwise supported, all herbal/ traditional products label shall state the following general cautionary statement, EXCEPT for product with indication for men’s health or product for children use only: “Pregnancy and breastfeeding: Insufficient reliable data” <p>- Amendment at 2.7.2 Specific Labelling Statements/ Warning & Precautions:</p> <p>a) For product containing Royal Jelly: Addition of “(for oral use)” after the word of “Royal Jelly”.</p> <p>b) Addition of new active ingredient i.e. “For product</p>	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<p>containing Propolis (for oral use), please state:</p> <ul style="list-style-type: none"> - “This product contains propolis and may cause severe allergic reactions including fatal anaphylactic reaction in susceptible individuals. - Asthma and allergy sufferers may be at a greater risk.” 	
7.	January 2013	Section A, 8.5.3 Certificate of Registration	<p>Updates according to the circular (100)dlm.BPFIK/PPP/01/03 Jld. 2, 21 January 2013: <i>Pemansuhan Pengeluaran Sijil Perakuan Pendaftaran Produk (SPP)</i>, i.e.:</p> <p>Form 1 (Certificate of Registration) for a product with the provisions, conditions, limitations and etc. of the registration, as stipulated in Regulation 8(8) of CDCR 1984, has been deleted from the regulation in year 2006 via amendment of PU(A) 336/06. Therefore, the certificate will no longer be issued by the Authority.</p> <p>Applicant shall refer to the product registration approval notification sent by the Authority or the Approved Product Registration List in NPCB website.</p>	<p>Circular (100)dlm.BPFIK/PPP/01/03 Jld. 2, 21 January 2013: <i>Pemansuhan Pengeluaran Sijil Perakuan Pendaftaran Produk (SPP)</i></p>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
1.	March 2013	Appendix 5, Guideline on Registration of Natural Products	<ul style="list-style-type: none"> - Replacement of information at 2.1.3 (c) ASEAN Harmonisation Negative List of Ingredients with (c) Ingredients (Botanicals and Substance Derived from Animals) which are banned due to safety reasons. - Renumbering of tables in the appendix. 	Memo from Sub-Section of Complementary Medicine (11)d/m.BPFFK/PPP/06/17 Jilid 30, 20 February 2013
2.	March 2013	Appendix 8: List of Permitted, Prohibited and Restricted Substances	<p><u>At 8.1.2 List of Restricted Active Ingredients and Combinations:</u></p> <p>Amendment on substance No. 16 Dextromethorphan from “Single Active Ingredient Tablet Formulation” to “Single Active Ingredient in Tablet Form, including lozenges”</p>	Drug Evaluation Committee No. 5/2013, 6 March 2013
3.	March 2013	Appendix 9: Labelling Requirements	<p><u>Amendment from:</u></p> <p>Patient Information Leaflet (PIL) or in <i>Bahasa Malaysia</i> known as <i>Risalah Maklumat Ubat Pesakit (RiMUP)</i>, is compulsory for products containing <u>scheduled poison</u> which are <u>self-administered</u> by patients.</p> <p>For details, please refer to <i>Direktif Penguatkuasaan Keperluan Mengemukakan Risalah Maklumat Ubat Pengguna (RiMUP) Bil. 5 Tahun 2011</i> Bil (15) d/m BPFFK/PPP/01/03 Jld 1 and Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna (RiMUP)</p>	Memo from Center for Post-Registration of Products (16)d/m.BPFFK/17/FV/14, 14 March 2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<p>PIL <u>may also be submitted for OTC products</u> in place of a package insert (PI). However, if the product is intended to be sold without a PI or PIL, the information required to being included in the PI or PIL shall be included in the unit outer carton of the product.</p> <p>The draft copy of the PIL in both version of English and <i>Bahasa Malaysia</i> shall be submitted for evaluation.</p> <p><u>Amendment to:</u></p> <p>Patient Information Leaflet (PIL) or in <i>Bahasa Malaysia</i> known as <i>Risalah Maklumat Ubat Pesakit (RiMUP)</i>, is compulsory for products which are <u>self-administered</u> by patients, including:</p> <ul style="list-style-type: none"> d) Scheduled poisons (Category A); e) Over-the-Counter, OTC products (Category X); f) Health supplements with high claims (disease risk reduction). <p>For details, please refer to:</p> <ul style="list-style-type: none"> iii) <i>Direktif Penguatkuasaan Keperluan Mengemukakan Risalah Maklumat Ubat untuk Pengguna (RiMUP) Bil. 5 Tahun 2011</i> Bil (15) dlm BPFK/PPP/01/03 Jld 1 iv) Garispanduan Pelaksanaan Risalah Maklumat Ubat untuk Pengguna (RiMUP) <p>The draft copy of the PIL in both English and <i>Bahasa Malaysia</i> shall be submitted for evaluation.</p>	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
4.	March 2013	Section D: Inspection & Licensing	<p><u>Addition of the paragraph and link:</u></p> <p>12.1 FOREIGN GMP INSPECTION</p> <p>PRH must provide acceptable evidence to show that the manufacturer of the product follows an internationally accepted standard of Good Manufacturing Practice (GMP) and recognized by the Authority in Malaysia.</p> <p>The Control of Drugs and Cosmetics Regulations 1984 (CDCR) requires that the standard of manufacture and quality control of medicinal products manufactured outside Malaysia is taken into consideration before the products are registered with the Authority. NPCB as the secretariat to the DCA is responsible to ensure all manufacturers of registered products in Malaysia are able to provide acceptable evidence that the manufacturing premises conform to current GMP requirements. Hence, foreign manufacturers are also subjected to GMP conformity assessments through acceptable GMP evidence or GMP inspection.</p> <p>For details and forms, please refer Guidance Document on Foreign GMP Inspection.</p>	Premises Inspection Evaluation Committee No. 3/2013, 14 March 2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
5.	March 2013	Section E: Post Registration Process	<p>Deletion of 'EMEA' and addition of 'Switzerland' in the following paragraph, as highlighted in yellow:</p> <p>16.4.2 VERIFICATION PROCESS</p> <p>For new indication which has been registered in European Countries / EMEA (United Kingdom, Sweden and/or France) and one of the other Authority's reference countries (United States of America, Australia, Canada, and Japan and Switzerland).</p>	Memo from Section of New Medicine (2)dIm.BPFK/PPP/06/17 Jilid 31, 13 March 2013
6.	March 2013	Appendix 2: Requirements for Product Registration	<p>Addition of the following paragraph:</p> <p>Effective 1st March 2013, biowaiver may be granted to generic immediate release oral solid dosage form products containing BCS Class I active ingredients listed in the Guidance On Biopharmaceuticals Classification System (BCS) – Based Biowaiver document. BCS Based biowaivers takes the three major factors that govern the rate and extent of drug absorption from immediate-release solid dosage forms into accounts i.e. solubility and permeability of the drug substance/ API, and dissolution characteristics of the dosage form. This BCS approach provides an opportunity to waive <i>in vivo</i> pharmacokinetic bioequivalence testing for certain categories of immediate-release drug products.</p> <p>(Directive <i>Arahan di Bawah Peraturan 29, Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984 Bil. 1 Tahun 2013</i>, 14 October 2011, 28 February 2013, Bil (101)dIm.BPFK/PPP/01/03 Jld 2).</p>	Memo from Sub-Section of Generic Medicine (7)dIm.BPFK/PPP/06/17 Jilid 31, 21 March 2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
7.	March 2013	<p>Appendix 5, Guideline on Registration of Natural Products</p> <p>*For Ginseng: Appendix 4, Appendix 5 and Appendix 9</p>	<p><u>2.4 Product Name</u></p> <p>Item No. 11: Issue: Addition of 'or referring to the profession'. Example: Addition of 'Herbalist, Doctor'.</p> <p>Addition of new item which is numbered as No. 13: Issue: Prohibited use of product names referring to any religious content Example: Maksum, Mahmudah, Arifbillah</p> <p><u>2.7 Labelling Requirement</u></p> <p>d) Example of label approved by the Authority Replacement with a new example.</p> <p><u>2.7.2 Specific Labelling Statements/ Warning & Precautions</u></p> <p>a) Amendment from:</p> <ul style="list-style-type: none"> For products containing GINSENG (including all Panax genus), please state: <ul style="list-style-type: none"> "Safe use of ginseng in pregnant women and children has not been established." "Do not exceed the stated dose." "Safety on long term use has not been established." <p>To:</p>	<p>Memo from Sub-Section of Complementary Medicine (24)dIm.BPFK/PPP/06/17 Jilid 31, 29 March 2013</p>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<ul style="list-style-type: none"> For products containing GINSENG (including all PANAX genus), please state: <ul style="list-style-type: none"> “Contraindicated in pregnant women.” “Safe use in lactating women and children has not been established.” “Do not exceed the stated dose.” “Safety on long term use has not been established.” b) Addition of the following: <ul style="list-style-type: none"> For product containing naturally occurring SALICYLIC ACID (e.g. Willow <i>Salix</i> spp.), please state: “People allergic to aspirin/ other NSAID should avoid this product.” For products containing GAMAT/ STICHOPUS spp. for ORAL USE ONLY, please state: “Please consult your pharmacist, doctor, or other healthcare providers about any other supplements/ medications you are taking and other health care problems. There may be a potential for interactions or side effects.” <p><u>2.7.4 Prohibited Visual/ Graphics/ Statement On Label Of Natural Products</u></p> <p>a) Amendment of the title 2.7.4 to the following: “Prohibited Visual/ Graphics/ Statement on Packaging</p>	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			Material (Label, Box, Package Insert or Patient Information Leaflet)" b) Addition of the following paragraph under this title 2.7.4: "General requirement: The graphics printed on outer and inner label has to be standardized to avoid confusion to the customers."	
1.	April 2013	Section E: Post-Registration Process	Replacement with the latest information at 16.3 Change of Product Registration Holder	Drug Control Authority Meeting No. 263, 29 April 2013
1.	May 2013	Section A: General Overview; 6. General Conditions for Registration of Drug Products under the Control of Drugs and Cosmetics Regulations 1984	Addition of link to specific circulars/ directives pertaining security label (hologram) as per listed below at 6.4 Product Authentication: a) "Circulars and directives pertaining to security label (hologram): i) Bil (32) dlm BPFK/02/5/1.3 ii) Bil (36) dlm BPFK/02/5/1.3 iii) Bil (62) dlm BPFK/02/5/1.3 iv) (88)dlm.BPFK/PPP/01/03 Jilid 2 v) (1)dlm.BPFK/PPP/07/25 Jld. 1 "	Circulars and directive as linked; latest directive (1)dlm.BPFK/PPP/07/25, 4 April 2013: <i>Pelaksanaan dan Pengendalian Label Keselamatan</i>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
2.	May 2013	Section B: Product Registration Process	<p>Addition of the following paragraph at 8.1.6 Second or Third Source:</p> <p>“A second source product, excluding biologic products, may differ for the following aspects:</p> <ul style="list-style-type: none"> a) equipments/ machines; b) minor manufacturing process (e.g. blending time, number of sub-parts); c) batch size; d) packaging materials, thickness of same packaging materials, pack sizes; <i>(Note: Use of different packaging material shall be supported with stability study report.)</i> e) manufacturer of API; and f) source of excipients. <p>EXCEPT differences in shape, embossment and thickness of tablet, in order to avoid change in product identity and subsequently causing confusion.</p> <p>The manufacturer shall declare with support of manufacturing validation process data that there is no change in formulation, specification of active ingredient(s) and excipient(s), and finished product for the second source product compared to the first source.</p> <p>For pharmaceutical product, no third source is allowed for same product unless in emergency situation such as outbreak of infectious disease.”</p>	Pharmacy Regulatory Policy Meeting No. 1/2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
3.	May 2013	Section C: Quality Control	<p>Replacement of this statement at 11. Guideline for the Submission of Product Samples for Laboratory Testing:</p> <p>“The sample shall be submitted to the Centre for Quality Control within 14 days after the payment has been confirmed. Application for product registration shall be rejected by the Authority if the sample is not submitted within 30 days from the date of confirmed payment.” (deleted)</p> <p>With the following:</p> <p>“The applicant is given a period of 14 days from the date of confirmed payment to send samples for laboratory testing. If the samples are not submitted within the specified time frame, the product registration application shall be tabled to the Authority for rejection.” (replacement)</p>	Pharmacy Regulatory Policy Meeting No. 1/2013
4.	May 2013	Section E: Post- Registration Process	<p>i) Addition of the following paragraph and link at 14. Maintenance of Registration:</p> <p>“For pharmaceutical products which were submitted for registration before 2009, applicants shall ensure that stability study for the products at zone IV B has been conducted and granted variation approval before submission of registration renewal application. Please refer circular (1)dIm.BPFIK/PPP/01/03Jld.3, 5 April 2013 for more information.”</p>	Circular (1)dIm.BPFIK/PPP/01/03 Jld. 3, 5 April 2013: Keperluan Data Kajian Stabiliti Dalam Zon IV B Bagi Produk Farmaseutikal Berdaftar

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
5.	May 2013	Section E: Post-Registration Process	<p>ii) Amendment of the following paragraph and addition of link at 17.2 POST-MARKET SURVEILLANCE</p> <p>a) It is the prime responsibility of the holder to ensure products marketed are in accordance to the standards and requirements of the Authority. Samples of products registered by the Authority may be taken and tested for compliance with official or pharmacopoeia standards or specifications agreed by the manufacturer;</p> <p>b) Samples of products Registered products by the Authority may be taken sampled and tested for compliance with official or pharmacopoeia standards or specifications agreed by the manufacturer. Labels and package inserts of the samples will also be checked to ensure compliance to the requirements as approved.</p> <p>c) The Authority will take necessary action on products which do not conform to the standards/ specifications and requirements in the form of warnings or recalls. If a sample fails to meet adequate specifications, the product registration holder will be issued a warning. Unless the failure is serious enough to justify recall of the product, The product registration holder has up to thirty (30) days to identify the source/ cause of quality defect and actions to be taken for to improvement quality.</p>	Memo from Center for Post Registration of Product Bil (87)dlm.BPFK/17/SV/21.16, 10 May 2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<p>17.2.1 PRODUCT COMPLAINTS</p> <p>a) The product registration holder should notify the NPCB Director of Pharmaceutical Services of any product quality related problems (with registered products) that the holder is aware of;</p> <p>b) It is also the responsibility of the prescribers, the pharmacists, as well as all other health professionals who come into contact with the drug to report to NPCB by using the NPCB complaint form i.e. BPFK 419 / BPFK 418.4 together with complaint sample (if any).</p> <p>c) All complaints received will be investigated by the NPCB as well as product registration holder/ manufacturer. It is the responsibility of the company to determine the appropriate corrective and preventive action.</p> <p>Guidelines on Good Distribution Practice, Chapter 9.</p> <p>17.2.2 PRODUCT RECALLS</p> <p>a) The decision for recalls of defective or unsafe a products shall be made when there is or may cause potential risk to the user of the products. Recalls may be done voluntarily by the product registration holder or as directed are instituted by the Authority, supported by the Director of Pharmaceutical Services Division, Ministry of Health Malaysia;</p>	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<p>b) The product registration holder is responsible for conducting recalls of defective or unsafe products. No recall should take place without first consulting/ informing the Authority. Director of Pharmaceutical Services.</p> <p>Guidelines on Good Distribution Practice, Chapter 10.</p>	
6.	May 2013	Appendix 4: Guideline on Registration of Health Supplement	<p>Replacement of this statement at 4.1.4 Exclusion as Health Supplement:</p> <p>“(iii) Any human part or substance derived from any part of the human body;” (deleted)</p> <p>With the following:</p> <p>“(iii) Any cells, tissues, organs or any substance derived from the human body;” (replacement)</p>	Pharmacy Regulatory Policy Meeting No. 1/2013
7.	May 2013	<p>Appendix 4: Guideline on Registration of Health Supplements;</p> <p>Appendix 5: Guideline on Registration of Natural</p>	<p>Addition of the following paragraph as “#” at column Outer Carton for Security Label (Hologram):</p> <p>“In case of no outer carton, the security label shall be applied to the immediate labels. The security label shall not be applied onto outer shrink wrap of a product.”</p>	<p>NPCB Dialogue with MOPI, PhAMA and MAPS on DRGD</p> <p>& Pharmacy Regulatory Policy Meeting No. 1/2013</p>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
		Products; Appendix 9: Labelling Requirements.		
8.	May 2013	Appendix 8: List of Permitted, Prohibited and Restricted Substances	<p>a) Amendment of the following at 8.1.2 List of Restricted Active Ingredients and Combinations:</p> <p>i) Camphor</p> <ul style="list-style-type: none"> - Existing: Oral; External (Analgesic >3%, Counter Irritant >11%) - Amendment: Oral; External (>11%) <p>ii) Menthol</p> <ul style="list-style-type: none"> - Existing: Analgesic: > 1.0%; Counter Irritant: >16% - Amendment: External Preparations >16% <p>b) Addition of the following substance in 8.1.1 (a) List of Prohibited Active Ingredients:</p> <p>1,3-dimethylamylamine (DMAA)</p>	Pharmacy Regulatory Policy Meeting No. 1/2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
9.	May 2013	Appendix 9: Labelling Requirements	<p>Amendment of the following requirement at 9.1.2 Proposed Package Insert:</p> <p>“Package insert (PI) is required for products containing scheduled poison and for injectable OTC products. PI <u>may</u> also be submitted for other OTC products. The draft copy of the PI shall be submitted for evaluation.”</p>	Drug Evaluation Committee Meeting No. 7/2013
10.	May 2013	<p>a) Appendix 11: Guideline On Filling The Online Application Form For Product Registration Via Quest System</p> <p>b) Two locations as follow: Appendix 4: Guideline on Registration of Health</p>	<p>a) Amendment of the following at 11.2.1 Step 1: Product Validation, [1] Product Name:</p> <ul style="list-style-type: none"> “Product name <u>shall not imply</u> the following: <ul style="list-style-type: none"> a. Tricky, confusion confusive and against the law; b. Scandal Scandalous and offensive; c. Prejudice Prejudicial; d. Well-known Notorious; e. * The name which may sound like or had been used for a product that has been revoked due to safety concerns; f. * Any other name which deemed inappropriate by the Authority. <p>* Note: “e” and “f” above is amended as follows:</p> <ul style="list-style-type: none"> “Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product or a product that has been revoked due to safety concerns is prohibited.” 	Drug Evaluation Committee Meeting No. 7/2013 & No. 8/2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
		Supplements, 4.5 Product Name; Appendix 5: Guideline on Registration of Natural Products, 2.4 Product Name.	<ul style="list-style-type: none"> “If a product name is found similar to another registered product or any other name which deemed inappropriate by the Authority, NPCB reserves the rights to request for the change of the product name.” <p>b) Addition of the following paragraph at these two locations:</p> <p>“Any product name which is the same or similar either in writing/ pronunciation, with the product name of an adulterated product is prohibited.”</p>	
11.	May 2013	Section E: Post- Registration Process	Addition of link to the directive and amendment of procedure at 16.3 Change of Product Registration Holder	Directive No. 4 Year 2013 (2)dIm.BPFFK/PPP/07/25, 3 Jun 2013: <i>Direktif Untuk Meminda Prosedur Pertukaran Pemegang Pendaftaran</i>
1.	June 2013	Section D: Inspection & Licensing	<p>Addition of the following information and link to the related circular at 12. Inspection:</p> <p><u>Additional Information:</u></p> <p>For manufacturing activity via campaign basis for carbapenem and monobactam product in area or manufacturing facility for cephalosporin product, please refer circular (1)dIm.BPFFK/30/06/2 Bhgn 2.</p>	Pharmacy Regulatory Policy Meeting No. 1/2013, 20 March 2013 and Circular from Centre for Compliance and Licensing (1)dIm.BPFFK/30/06/2 Bhgn 2, 23 May 2013: <i>Surat pekeliling berhubung</i>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
				<i>kebenaran mengilangkan keluaran-keluaran carbapenem dan monobactam di dalam fasiliti pengilangan keluaran-keluaran Cephalosporin</i>
2.	June 2013	Section E: Post-Registration Process	Amendment at 16.1 Variation based on the directive on implementation of Malaysian Variation Guideline (MVG)	Memo from Centre for Post-Registration of Product, (3)dlm.BPFK/17/VF/8 Jilid 9, 18 June 2013
3.	June 2013	Appendix 2: Requirements for Product Registration	Addition of link to related circular at 2.1.3 Additional Information on Bioavailability/ Bioequivalence: For modified-release products , dosage recommendations and regime must be supported by bioavailability studies.	Circular (3)dlm.BPFK/PPP/01/03 Jld. 3, 12 June 2013: <i>Keperluan Akreditasi Pusat Kajian Bioavailability/ Bioekuivalens Bagi Produk Dalam Bentuk Modified Released</i>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
4.	June 2013	Appendix 8: List of Permitted, Prohibited and Restricted Substances	<p>Amendment of the following and addition of link to related circular at 8.2 List of Prohibited and Restricted Excipients:</p> <p><u>Additional Information</u></p> <p>3. Methylene Chloride/ Dichloromethane <u>are not allowed</u> as solvent in film-coating for locally manufactured products. in order to protect workers during manufacturing process.</p> <p>For detail on implementation, please refer circular (2)dIm.BPFIK/30/06/2 Bhgn 2.</p>	<p>Pharmacy Regulatory Policy Meeting No. 1/2013</p> <p>and</p> <p>Circular from Centre for Compliance and Licensing (2)dIm.BPFIK/30/06/2 Bhgn 2, 23 May 2013: <i>Surat pekeliling berhubung larangan penggunaan methylene chloride atau dichloromethane (DCM) dalam proses pengilangan produk tempatan</i></p>
5.	June 2013	Appendix 9: Labelling Requirements	<p>a) Addition of the following information at 9.1.3 Patient Information Leaflet after the last paragraph “The draft copy of the PIL in both English and <i>Bahasa Malaysia</i> shall be submitted for evaluation”:</p> <p>“Note: <i>PIL is not compulsory to be sold with the product but will be uploaded onto NPCB website as reference for patients or consumers.</i> <i>For OTC Products, if the product is intended to be sold without a PI or PIL, the information required to be included in the PI or PIL shall be printed on the unit outer-carton of</i></p>	<p>a) Memo from Section of Generic Medicine, Centre for Product Registration, Bil (10)dIm.BPFIK/PPP/06/ 17 Jld. 34, 6 June 2013</p>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<p><i>the product.”</i></p> <p>b) Addition of information on products containing Trimetazidine and link to related circular at 9.2 Specific Labelling Requirements.</p>	<p>b) Directive No. 5 Year 2013 (4)dlm.BPFIK/PPP/07/25, 3 June 2013: <i>Direktif untuk menghadkan penggunaan produk mengandungi Trimetazidine dan mengukuhkan amaran berkaitan dengan risiko kesan advers simptom parkinson pada sisip bungkusan semua produk Trimetazidine</i></p>
6.	June 2013	Appendix 10: Guideline on Patient Dispensing Pack for Pharmaceutical Products in Malaysia	<p>Amendment as follows at Table 2: Dermatological Preparations Maximum Pack Size Recommendations For Pharmaceutical Products</p> <p>D07A Corticosteroids, plain</p> <p>D07AC Corticosteroids, potent (group III):</p> <ul style="list-style-type: none"> - Max 15g to 100g <p>D07AD Corticosteroids, very potent (group IV):</p> <ul style="list-style-type: none"> - Max 15g to 100g 	<p>Directive Bil (4) dlm BPFIK/PPP/01/03 Jld 1: <i>Justifikasi Untuk Perubahan Pek Saiz Pesakit Untuk Penyakit Kulit Tertentu Bagi Produk-Produk Dematologi</i></p>

NO.	REVISION	UPDATES		REFERENCE				
		SECTION/ APPENDIX	DETAILS					
			**Note: Pack size of 500g is allowed for hospitals and skin specialist clinics use.					
1.	July 2013	Appendix 5: Guideline on Registration of Natural Products	<p>a) Addition of the following information in Table 7 Product Names Which Are Not Permitted To Be Registered:</p> <table><tr><th>Non-Permissible Product Names</th><th>Example</th></tr><tr><td>Name of internal organ</td><td>Example: Liver, Brain, Kidney, etc.</td></tr></table> <p>b) Addition of the following information (as highlighted in yellow) under 2.5.3 Quality Testing For Specific Ingredient:</p> <p>ii) For products containing Red Yeast Rice (<i>Monascus purpureus</i>), applicants shall provide certificates of analysis (for both raw material and finished product) showing the Monacolin-K content. The percentage of Monacolin-K shall not exceed 1% and the Monakolin-K consumed shall not exceed 10 mg per day.</p>	Non-Permissible Product Names	Example	Name of internal organ	Example: Liver, Brain, Kidney, etc.	<p>Memo from Sub-Section of Complementary Medicine (1)dlm.BPFK/PPP/06/17 Jilid 35</p> <p>Drug Evaluation Committee Meeting No. 12/2013 [c] For products containing Psyllium/ Plantago (Seed/ Husk)]</p>
Non-Permissible Product Names	Example							
Name of internal organ	Example: Liver, Brain, Kidney, etc.							

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<p>c) Addition of the following information (as highlighted in yellow) under 2.7.2 Specific Labelling Statements/ Warning & Precautions:</p> <ul style="list-style-type: none"> For products containing Senna Leaf (Cassia spp.) – fruit/ pod/ semen and leaf and Rhubarb/ Radix et Rhizoma Rhei/ Rheum Palmatum/ Rheum Officinale – root part, please state: <ul style="list-style-type: none"> “Do not use when abdominal pain, nausea or vomiting is present.” “Frequent or prolonged use of this preparation may result in dependence towards the product and ‘imbalanced electrolytes’.” “Please consult a healthcare practitioner for use beyond 7 days.” For products containing Psyllium/ Plantago (Seed/ Husk), please state: <ul style="list-style-type: none"> “If the constipation does not resolve within 3 days or if abdominal pain occurs or in case of any irregularity of faeces, the use of psyllium should be discontinued and medical advice must be sought.” “Please consume a large amount of fluid/ water when taking this product.” 	

NO.	REVISION	UPDATES		REFERENCE				
		SECTION/ APPENDIX	DETAILS					
2.	July 2013	Appendix 8: List of Permitted, Prohibited and Restricted Substances	Amendment on Cyclamates under 8.2 List of Prohibited and Restricted Excipients: <ul style="list-style-type: none">- Deleted from 8.2.1 List of Prohibited Excipients.- Added in 8.2.2 List of Restricted Excipients as follows:<table><tr><th>Excipients</th><th>Restrictions</th></tr><tr><td>Cyclamates</td><td>Limited to not more than 1.5mg/kg body weight/day</td></tr></table>	Excipients	Restrictions	Cyclamates	Limited to not more than 1.5mg/kg body weight/day	Drug Evaluation Committee Meeting No. No. 12/2013, 25 June 2013 & Memo from Sub-Section of Complementary Medicine (55)dIm.BPFK/PPP/06/17 Jilid 34
Excipients	Restrictions							
Cyclamates	Limited to not more than 1.5mg/kg body weight/day							
1.	August 2013	Section A: General Overview	a) Addition of the following information under 5.1.3 Registration Of Product For Export Only (FEO) <ul style="list-style-type: none">- Applications for registration of FEO products are processed based on abridged evaluation.- Applications shall be submitted by using an application form BPFK 438.1(for Generic Medicines/ Health Supplements) and BPFK 438.1 (T) (for Complementary Medicines).	Drug Evaluation Committee Meeting No. 14/2013				

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			<p>b) Addition of the following information under 6. General Conditions For Registration Of Drug Products Under The Control Of Drugs And Cosmetics Regulations 1984, 6.1 Registration Number:</p> <p>Registration number appears as MALYYMM\$\$\$\$@##, e.g. MAL11070001ACERS:</p> <ul style="list-style-type: none"> - MAL refers to “Malaysia” - YYMM refers respectively to year and month of registration by the Authority (e.g. 1107: July 2011); - \$\$\$\$ refers to a serial number for a product being registered (e.g. 0001); - @ refers to category of product being registered i.e. A/ X/ N/ T/ H; and - ## refers to administrative code used by NPCB i.e. C/ E/ R/ S. - The symbols @ and ## refer to: <ul style="list-style-type: none"> a) A= Scheduled Poison b) X= Non-scheduled Poisons c) N= Health Supplements d) T= Natural Products/ Traditional Medicines e) H= Veterinary Products f) C= Contract Manufactured (the product is manufactured by a GMP certified contract manufacturer) 	Pharmacy Regulatory Policy Meeting No. 2/2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
			g) E= For Export Only (FEO) (the product is to be sold for export only and not for sale in the local market) h) R= Repacked (the product is repacked by an approved GMP certified repacker) i) S= Second source (the product from a second source/ approved second manufacturer)	
			c) Addition of the following information (as highlighted in yellow) under 1.3.2 Classification of FDI Products, a) Main Criteria, no. ii) and 1.3.3 Pictorial Guide to Classification of Food-Drug Interface Products: Substances or ingredients used for therapeutic purposes shall not be added to food: <u>Glutathione, Hyaluronic Acid, Red Yeast Rice, Natto Extract, Placenta, Bile, GABA, Resveratrol And Glucosamine</u>	Circular (4)dlm.BPFFK/PPP/01/03 Jld. 3, 5 August 2013: <i>Keperluan Pendaftaran Produk Food-Drug Interface (FDI) yang mengandung bahan aktif red yeast rice, natto extract, placenta, bile, glucosamine, hyaluronic acid, glutathione, GABA, resveratrol</i>

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
2.	August 2013	Section B: Product Registration Process	<p>a) Amendment of the following paragraph (addition of information as highlighted in yellow) under 8.3.1 Screening of Application - Satisfactory:</p> <p>Upon screening approval, the applicant is requested to proceed for payment and submission of hard copy documents (if applicable).</p> <p><u>Submission of hard copy documents:</u></p> <p>Please refer Table under 8.3.1.</p> <p>For payment, applicant shall print three (3) copies of payment voucher and submit two (2) copies of printed payment voucher together with appropriate fees to the Finance Department, NPCB for payment confirmation. The applicant is advised to keep a copy of the payment voucher as reference. A product reference number shall be given to the application upon payment confirmation.</p> <p>Applicant shall make Payment has to be made within thirty (30) days from the date of approval for screening. The application form will be deleted from the system if payment has not been made within this stipulated time.</p>	NPCB Dialogue with MOPI, PhAMA and MAPS on DRGD 2013

NO.	REVISION	UPDATES		REFERENCE						
		SECTION/ APPENDIX	DETAILS							
			<div><div>b) Amendment under 8.4.4 Timeline for Product Registration</div><table><tr><th>(B)</th><th>Abridged Evaluation</th><th>*Duration (Inclusive screening process)</th></tr><tr><td>5.</td><td>Generics (Non-Scheduled Poison) (Product categories as stated in Table V above) a) Single active ingredient b) Two (2) or more active ingredients</td><td> a) 116 working days b) 136 working days</td></tr></table></div>	(B)	Abridged Evaluation	*Duration (Inclusive screening process)	5.	Generics (Non-Scheduled Poison) (Product categories as stated in Table V above) a) Single active ingredient b) Two (2) or more active ingredients	 a) 116 working days b) 136 working days	Memo from Section of Generic Medicine (27)dIm.BPFK/PPP/06/17 Jilid 36
(B)	Abridged Evaluation	*Duration (Inclusive screening process)								
5.	Generics (Non-Scheduled Poison) (Product categories as stated in Table V above) a) Single active ingredient b) Two (2) or more active ingredients	 a) 116 working days b) 136 working days								
3.	August 2013	Appendix 8: List of Permitted, Prohibited And Restricted Substances	<div><div>Addition of the following combination under b) Prohibited Combinations, 8.1.1 List Of Prohibited Active Ingredients And Combinations:</div><div>Topical Preparation Containing Combination of Antibiotic, Antifungal and Steroid</div></div>	Pharmacy Regulatory Policy Meeting No. 2/2013						

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
4.	August 2013	Appendix 9: Labelling Requirements	<p>a) Addition of the following information (as highlighted in yellow) under 9.1.1 Label (Mock-Up) For Immediate Container And Outer Carton</p> <p>* Exempted for small labels (i.e. 5ml and less) such as used for ampoules/ cartridge, and vials, eye drops, ear drops, and nose drops.</p>	Pharmacy Regulatory Policy Meeting No. 2/2013
			<p>b) Addition of the following information under Additional Information, 9.1.1 Label (Mock-Up) For Immediate Container And Outer Carton:</p> <p>Use of QR code is permitted only for the purpose of monitoring inventory of the product, such as batch number, expiry date and manufacturing date, BUT NOT for linkage to any website. The addition of QR code on registered product labels without variation approval from NPCB can be considered only if that is the only proposed change to the currently approved labels.</p>	

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
1.	November 2013	Section E: Post-Registration Process	Addition of link to the following circular under 14. Maintenance of Registration (5)dIm.BPFIK/PPP/01/03	Circular (5)dIm.BPFIK/PPP/01/03 Jld. 3, 14 August 2013: <i>Lanjutan Tarikh Kuatkuasa Untuk Memenuhi Keperluan Data Kajian Stabiliti Dalam Zon IV B Bagi Produk Farmaseutikal Berdaftar</i>
2.	November 2013	Section E: Post Registration Process	Replacement of this statement at 16.4.2 VERIFICATION PROCESS: “For new indication which has been registered in European Countries (United Kingdom, Sweden and/or France) and one of the other Authority’s reference countries (United States of America, Australia, Canada, Japan and Switzerland).” (deleted) With the following: “For new indication which has been registered by <u>any two</u> reference country’s authorities (United Kingdom, Sweden, France, United States of America, Australia, Canada, Japan, Switzerland and EMA).” (replacement)	Pharmacy Regulatory Policy Meeting No. 3/2013

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
3.	November 2013	Appendix 2: Requirements For Product Registration	<p>Addition of the following paragraph under B) BIOEQUIVALENCE (BE) STUDY:</p> <p>Note: The two above directives shall be read in conjunction with the supplementary circular that further explains the procedure for evaluation of BE centre inspection reports in line with the requirement of accreditation of BE Centres. (Reference: Circular dated 12 September 2013; Bil(6)dIm.BPFFK/PPP/01/03 Jld 3.)</p>	<p>Memo from Section of Generic Medicine (15)dIm.BPFFK/PPP/06/17 Jilid 37 & Circular (6)dIm.BPFFK/PPP/01/03 Jld. 3</p>
4.	November 2013	<p>Appendix 4: Guideline on Registration of Health Supplements;</p> <p>Appendix 5: Guideline on Registration of Natural Products;</p> <p>Appendix 9: Labelling Requirements.</p>	<p>Amendment of the following paragraph under labelling requirement of Appendix 4 and Appendix 5 as well as Table 1 in Appendix 9:</p> <p>To declare source of ingredients derived from animal origin (active and excipient) including starting materials and gelatine (capsule shell), including gelatin (active, excipient, and/or capsule shell)</p>	<p>Drug Evaluation Committee Meeting No. No. 17/2013</p>

NO.	REVISION	UPDATES		REFERENCE				
		SECTION/ APPENDIX	DETAILS					
5.	November 2013	Appendix 5: Guideline on Registration of Natural Products	<p>a) Addition of the following allowance limit at 2.2 Excipient:</p> <p>LIST OF RESTRICTED EXCIPIENTS:</p> <table><tr><th>Specific Excipient</th><th>Limits (Not allowed)</th></tr><tr><td>2. Menthol</td><td>- Oral (>10mg/day) - External (>10%)</td></tr></table> <p>b) Addition of the following paragraph at 2.4 PRODUCT NAME and amendment in Table 7 Non-Permissible Product Names:</p> <p>“For products in which the product name is the name of active ingredient or the product name is a common name, e.g. <i>Kapsul Kacip Fatimah</i>; <i>Misal Kucing Tea</i>; <i>Ortosiphon Capsule</i>; <i>Herbal Rub</i>; <i>Natural Herb Capsule</i>, a brand name shall be added to the product name, in order to differentiate and identify this specific product.”</p> <p><i>Note: Please refer amendment in Table 7 Non-Permissible Product Names in Attachment.</i></p>	Specific Excipient	Limits (Not allowed)	2. Menthol	- Oral (>10mg/day) - External (>10%)	Memo from Section of Complementary Medicine (56)dIm.BPFG/PPP/06/17
Specific Excipient	Limits (Not allowed)							
2. Menthol	- Oral (>10mg/day) - External (>10%)							

NO.	REVISION	UPDATES		REFERENCE					
		SECTION/ APPENDIX	DETAILS						
6.	November 2013	Appendix 5: Guideline on Registration of Natural Products	c) Amendment of the following statements (addition as highlighted with yellow) under 2.7.4 Prohibited Visual/ Graphics/ Statement On Packaging Material (Label, Box, Package Insert Or Patient Information Leaflet)						
			<table><tr><th>No.</th><th>Subject Matter</th><th>Example(s)</th><th>Notes</th></tr><tr><td>10.</td><td>Introduction/ description of founder/ manufacturer i.e. elaboration on the identity of the founder or manufacturer</td><td>Manufacturer ABC is a GMP certified manufacturer and has manufactured many products. Founder Dr. ABC is a world renowned surgeon.</td><td>Prohibited on product label</td></tr></table>	No.	Subject Matter	Example(s)	Notes	10.	Introduction/ description of founder/ manufacturer i.e. elaboration on the identity of the founder or manufacturer
No.	Subject Matter	Example(s)	Notes						
10.	Introduction/ description of founder/ manufacturer i.e. elaboration on the identity of the founder or manufacturer	Manufacturer ABC is a GMP certified manufacturer and has manufactured many products. Founder Dr. ABC is a world renowned surgeon.	Prohibited on product label						

NO.	REVISION	UPDATES		REFERENCE
		SECTION/ APPENDIX	DETAILS	
7.	November 2013	Appendix 9: Labelling Requirements	<p>Addition of the word 'parenteral' in the following statement under 9.2 Specific Labelling Requirements, No. 20 – Benzyl Alcohol:</p> <p>The following <u>statement</u> shall be <u>included on label and in package insert</u> of parenteral products containing benzyl alcohol:</p> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>As this preparation contains benzyl alcohol, its use should be avoided in children under two years of age. Not to be used in neonates.</p> </div>	Pharmacy Regulatory Policy Meeting No. 3/2013