APPENDIX 25

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 for POA content whilst details of specific requirements are illustrated according to the test category.

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 States Pharmacopeia (USP) shall be used as the main references.
iv) All tests and its specification listed in BP and/or USP in General Monographs and Specific Monographs 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 specific 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.

2. SPECIFIC REQUIREMENTS

The specific requirements for test methods are based on type of tests and dosage forms of product as stated 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	a. Dissolution parameters should include: i) type of apparatus ii) type and volume of dissolution medium iii) rotation rate iv) temperature of solution v) sampling time b. Complete formula for calculation especially for extended and delayed release products. c. Method of analysis for example HPLC, UV, etc.

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) iii) Test for Media Sterility and

Categories	Type of Tests	Specific Requirements
		Growth Promotion Test iv) Dilution schemes for test and standard solutions. • 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	Bacterial Endotoxins Test (BET) or Limulus Amebocyte Lysate (LAL) Test	a. Certificate of analysis for endotoxin and LAL (limulus amebocyte lysate) reagent b. List of depyrogenated or pyrogen-free apparatus, glassware and reagent c. Detailed preparation of standard solutions, LAL reagent/ substrate, sample d. Detailed calculation for determination of maximum valid dilution (MVD) e. The product's endotoxin limit concentration (ELC) and source of information f. Detailed calculation for determination of endotoxin limit concentration if the ELC is not in BP, USP, JP or EP g. Detailed test procedure h. Calculation and interpretation of test result
	Sterility Test	a. List of media and reagent i) Culture media ii) List of rinsing solution, buffer solution and diluent

Categories	Type of Tests	Specific Requirements
		iii) Neutralizing agent (if any) b. Preparation of media & Composition of Rinsing Buffer c. Preparation of test sample (including steps to eliminate antimicrobial activity due to antibiotic samples or samples which contain preservatives). d. Detailed test procedure for sterility test i) Quantity of sample/ Volume of sample ii) Membrane filtration/ Direct inoculation iii) Open System or Closed System (if uses Membrane filtration method) iv) Volume of rinsing fluid v) Volume of media used vi) Incubation time and temperature

Categories	Type of Tests	Specific Requirements
	Microbial Contamination Test	Required for ALL non-sterile products a. Preparation of test sample (including neutralizing of preservatives for samples that contain preservatives) b. Total Viable Aerobic Count • Detailed test procedure for Total Aerobic Microbial Count (TAMC) and Total Yeasts and Molds Count (TYMC) by Plate Count, Membrane Filtration or Most-Probable Number (MPN) method. c. Test for Specified Microorganisms • Detailed test procedure for each specific microorganism tested (including identification and confirmation test) • Specification and acceptance criteria For details, please refer to: *Bil. (4) dlm. BPFK/PKK/12/05*. *Maklumat Lanjutan Tentang Spesifikasi Baru Untuk Ujian Kontaminasi Mikrobial* (30 March 2010)
	Quality Testing for Specific Ingredient	For a product containing specific ingredient such as Aphanizomenon flos aquae, Red Yeast Rice (Monascus purpureus), ingredient(s) derived from seafood and placenta, please refer to **Appendix 6** and **Appendix 7** for the testing requirement(s).

Note:

1. Finished product testing shall be conducted on every batch produced as per approved finished product specifications.
2. Manufacturer shall ensure that products manufactured locally or overseas are free from any contamination of *Burkholderia cepacia*. Please refer to this circular for details:
   Bil. (90) dlm.BPFK/PPP/01/03/ Jld. 2
   Ujian Kontaminasi Burkholderia cepacia (19 December 2012)
3. Products are not allowed to send for gamma radiation treatment for the control of microbial contamination. Please refer to this circular for details:
   Bil. (54) dlm.BPFK/02/5/1.3.
   Aktiviti Pendedahan Produk Berdaftar kepada Sinar Gamma (18 April 2006)