REGISTRATION GUIDELINE OF VETERINARY PRODUCTS (REGOVP)

National Pharmaceutical Control Bureau
Ministry of Health, Malaysia

Version 2-Dec 2009

PREAMBLE

This "**REGISTRATION GUIDELINE OF VETERINARY PRODUCTS (REGOVP)**" will serve as the reference guide for registration of pharmaceutical products for animal use.

The contents of this version include:

- Information relating to administrative requirements and procedures.
- Information on Drug Control Authority (DCA) policies currently applicable.
- Guidelines on the online application process and requirements which will incorporate the ASEAN technical requirements and standards for pharmaceuticals (where applicable).

An on-going review of policy matters will continue, taking into account the global regulatory environment, to allow for timely and pertinent changes.

Please visit the National Pharmaceutical Control Bureau (NPCB) website at http://www.bpfk.gov.my for updates in regulatory information.

List of amendments / changes:

December 2009 Revision

Section 1

2.2

vi) added clarification for product containing Biologics in combination with scheduled poisons

vii) added clarification for product containing Pesticides in combination with scheduled poisons

2.6

Added clarification on the Exemption List on Vitamins, Amino Acids, Minerals, Electrolytes & Others For Manufacturing Purpose Only

5.2 Stop Clock

Amended 4 months to 6 months

Appendix 7 : Exemption List as Single Ingredients of Vitamins, Amino Acids, Minerals, Electrolytes & Others For Manufacturing Purpose Only

Update list of Vitamins, Amino Acids, Minerals, Electrolytes & Others without the percentage

Appendix 10 : List of Ingredients (Active) Not Allowed to be Registered By the DCA

Added clarification for **B. Ingredients not allowed for food-producing animals** to include **Aquacultures**

Appendix 11 : Guideline For Stability Data

Update clarification for **8. Duration of stability trials for i) Locally manufactured product**

Appendix 12 : Allowable Maximum Residual Limit (MRL)

Added List of **MAXIMUM PERMITTED PROPORTION OF DRUG RESIDUES IN AQUACULTURE AND ALLOWABLE WITHDRAWAL PERIOD**

Addition of Appendix 14 : Regulation of Veterinary Products in Malaysia

March 2009 Revision

GUIDELINE TITLE

Amended Registration Guidance Document For Veterinary Products to Registration Guideline Of Veterinary Products [REGOVP]

SECTION 1

2.2

vi) added clarification of veterinary biologics .

vii) amended Pesticides ……Pesticides Act 1974 to Pesticides applied externally

X) added Cosmetics for animals

Xi) added Disinfectant for animals

2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10

addition of these paragraphs to interpret paragraph 2.1 and 2.2.

3.1(i)

removed statement of "containing existing chemical entity(s) in a new dosage form"

4.3.2

added clarification of GMP certificate requirements. "[3]DCA will usually …….will need to be provided"

added clarification of FAMI-QS

13.4

addition of statement for notification procedure for products other than Scheduled Poison

13.7

moved from paragraph 13.11

13.9

moved to paragraph 2.9

13.10

moved to paragraph 2.11

13.11

Moved to paragraph 13.7

13.12

Moved to Appendix 11, no 8

Appendix 5

Moved to Appendix 10 with addition of list of ingredients not allowed to be registered by the DCA

C. Any products containing of Chlorofluorocarbon

D. Combinations of herbal/natural with other drugs

Appendix 6

Moved to Appendix 5

Addition of Appendices as below:

Appendix 6	Ingredient that affect the characteristic of feed
Appendix 7	Exemption list as single ingredient on vitamins, amino acids & minerals
Appendix 8	Indication and functional claims for Health/Dietary Supplement Product
Appendix 9	List of Prohibited Botanicals (Herbs and Herbal Derivatives)
Appendix 10	List of Ingredients (active) not allowed to be registered by the Drug Control Authority
Appendix 11	Guideline for Stability Data
Appendix 12	Allowable Maximum Residual Limit (MRL)
Appendix 13	Classification of Ingredients for Veterinary Use

SECTION 2

STEP 1

Addition of Check List for Data Entry of Product Validation.

STEP 2

Section D :
Removed the word “medicine” from parameter 19-The words” Keep medicine out of reach……..or English.
Addition of parameter 21 for Herbal/Natural products
Addition of parameter 25 for Scheduled Poison products

Addition of Check List for Data Entry of Part 1, Part S and Part P

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SECTION 1
GENERAL OVERVIEW OF THE DRUG REGISTRATION SYSTEM IN MALAYSIA (INCLUDING ADMINISTRATIVE PROCEDURES)

SECTION 1

1. INTRODUCTION

1.1 The Control of Drugs and Cosmetics Regulations 1984 was gazetted in June 1984, with the establishment of the Drug Control Authority (DCA) as the licensing authority. The daily operations of drug and cosmetic registration, together with the attendant monitoring and surveillance activities have been delegated to the National Pharmaceutical Control Bureau (NPCB).

1.2 The guidelines outlined in this document are primarily drawn up in accordance to the legal requirements of the **Sale of Drugs Act 1952** and the **Control of Drugs and Cosmetics Regulations 1984.** While every effort has been made to include the legal requirements of other related legislation, wherever possible, applicants are reminded that it is still their responsibility to ensure that their products duly comply with the requirements of these legislation, namely:-

(i) **Dangerous Drugs Act 1952**;

(ii) **Poisons Act 1952**;

(iii) **Medicine (Advertisement & Sale) Act 1956**;

(iv) **Patent Act 1983**; and also

(v) Any **other relevant Acts.**

1.3 Paragraph 7(1)*(a)* of the **Control of Drugs and Cosmetics (Amendment) Regulations 2006** requires all products to be registered with the DCA prior to being manufactured, sold, supplied, imported, possessed or administered, unless the product is exempted under the specific provisions of the Regulations.

A 'product' as defined in the Regulations means

(a) a drug 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 purpose;

(b) a drug to be used as an ingredient of a preparation for a medicinal purpose; or

(c) a cosmetic"

Any change to the above defined parameters may result in the need to apply for a new product registration or an application for approval of an amendment (variation) to the existing product registration.

1.4 Applicants are encouraged to be familiar with the contents of these guidelines and the governing legislation before they submit applications for product registration.

2. DRUG REGISTRATION

2.1 Any ***drug*** which 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 animals*, whether internally or externally, for a *medicinal purpose* is required to be registered with the DCA.

Medicinal purpose means any of the following purposes:

(i) alleviating, treating, curing or preventing a disease or a pathological condition, or symptoms of a disease;

(ii) diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;

(iii) contraception;

(iv) inducing anaesthesia;

(v) maintaining, modifying, preventing, restoring or interfering with, the normal operation of a physiological function;

(vi) controlling body weight;

(vii) general maintenance or promotion of health or well-being.

A SEPARATE REGISTRATION GUIDANCE DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICAL PRODUCTS FOR HUMAN USE IS AVAILABLE.

2.2 The Regulations do not apply to the following products :-

(i) diagnostic agents and test kits for laboratory use;

Diagnostic agents/test kits for laboratory use must be labelled '**FOR LABORATORY USE ONLY**'. Products which are not labelled as such shall be deemed to be for human or animal use and need to be registered with the DCA.

(ii) non-medicated medical and contraceptive devices;

(iii) non-medicated bandages, surgical dressings, plaster, dental fillings;

(iv) instruments, apparatus, syringes, needles, sutures, catheters;

(v) **Food** - as defined under the Food Act 1983 and Food Regulations 1985.

(vi) **Animal Vaccines and Biologics** which is currently controlled under Animal Act 1953 (Revised 2006) (Section 30 and 84)

"Veterinary biologics" means animal vaccines, serum, plasma, toxin and anti-toxins, toxoids, antigens and any substance or mixture or substances live, killed or attenuated derived from animals, birds, parasites or micro-organisms or parts thereof

[including products containing hormone (natural/synthetic), yeast, probiotics or enzymes either in single or in combination with other active substance/s**]**

However, products containing these ingredients in combination with scheduled poisons, they will be regulated under the DCA

(vii) **Pesticides applied externally**

"pest" includes bacteria, virus, fungi, weeds, insects, rodents, birds, or any other plant or animal that adversely affects or attacks animals, plants, fruits or property

For products containing pesticide ingredients in combination with scheduled poisons, they will be regulated under the DCA

(viii) **Animal feed** (does not include medicated premixes)

(ix) **Ingredients that affect the characteristic of feed** (preservatives and mould inhibitors, antioxidants, binders, stabilisers, anticaking agents, gelling agents, acidity regulators, colourants, flavouring agents, etc) See Appendix 6 for such substances that affect the characteristic of feed where registration is not required.

(exception for products containing a combination of acidity regulators with other active substances)

(x) **Cosmetics for animals**

A cosmetic product shall mean "any substance or preparation intended to be placed in contact with various external parts of the animal body or with teeth and the mucous membranes of the oral cavity, with a view exclusively or mainly to cleaning them, perfuming them,changing their appearance and/or correcting body odours and/or protecting them or keeping them in good condition

(Xi) **Disinfectant**

"Disinfectant" means a substance:

a) that is recommended by its manufacturer for application to an **inanimate object** to kill a range of micro-organisms; and

b) that is not represented by the manufacturer to be suitable for internal use

2.3 Animal feed which contains drug(s) is exempted from the registration requirements until a separate regulatory control is established.

2.4 The implementation of the Regulations on veterinary products shall be on all products containing Scheduled poison(s) as defined in the Poisons Act 1952 and which do not contain scheduled poison, including premixes, dietary/health supplements or herbal/natural preparations intended to be administered to animals for **medicinal purpose.**

2.5 Premixes for medicinal purpose

Premixes are defined as:

Mixtures of one or more active ingredients, usually in suitable bases, that are prepared to facilitate feeding the active ingredients to animals. They are used exclusively in the preparation of animal feed for medicinal purpose.

Premixes occur in granulated, powdered, semi-solid or liquid form.

May occur in pelleted form.

Premixes for medicinal purpose are registrable

2.6 Dietary/health supplements shall mean 'products that are intended to supplement the diet taken by mouth in the forms such as pills, capsules, tablets, liquids or powders and not represented as conventional food/sole item of a meal or diet'.

Dietary/ Health Supplements may include ingredients such as: vitamins, minerals, amino acids or natural substances of plant/animal origin, with nutritional/physiological function.

Exemption list (will not require registration) as single ingredient on vitamins, amino acids, minerals, electrolytes and others which will be used for manufacturing purpose only see Appendix 7

For allowable indication and functional claims see Appendix 8.

2.7 Herbal/Natural products are products that:

- only contain ingredients which are obtained or extracted from plants and that are not highly purified or characterised; and
- only make **general health claims**, NOT specific therapeutic claims that refer to prevention (or reduction), cure or alleviation of a specific disease or condition; and
- are only administered orally or topically on the skin, NOT parenterally (eg by injection), or applied topically to tissue other than skin (eg eye, nose or throat).

"General health claims" are those that refer to possible health benefits for anatomical organs or physiological systems within animals without mentioning specific diseases or conditions.

- The label must clearly state as the first statement "This product is registered as a Herbal/Natural Product"; followed by

- "May be of benefit for improving/promoting [*organ/system*]health"

Therapeutic claims are not allowed in Herbal/Natural products.

For List of Prohibited Botanicals See Appendix 9

2.8 Dietary/health supplements making a therapeutic claim/indication are considered as Non-Poison (OTC) product. Scientific evidence and efficacy data will be required for the registration of any therapeutic claim.

2.9 Scheduled Poison and OTC substance in soluble powder to be added to drinking water and/or animal feed which may contain one or more active ingredients **with excipients** intended for oral administration for medicinal purpose need to be registered.

The directions for use are a mandatory labelling requirement.

However, raw material containing scheduled poison and OTC substance shall not considered for registration, and such raw material is not allowed to be used by the end user

End user include in-farm (Cattle, Poultry, Swine etc) self-mixers or home mixers of animal feed and **feed millers**

2.10 **Combination Products**

(For list of combination not allowed to be registered by the DCA see Appendix 10)

A combination product must provide advantage over and above that which can be obtained by the use of monosubstance preparations. Information and data to demonstrate that the combination of active ingredients provides a benefit that cannot be obtained by the use of each of the active ingredients individually (i.e., each active ingredient has made a contribution) is required.

When 3 or more active ingredients are used in the same combination, the resulting benefit from the use of the combination must be a benefit that cannot be obtained from combinations involving a lesser number of active components than the number contained in the full combination (e.g., a 3-way combination must be better than all possible 2-way combinations of the same 3 actives).

This demonstration of benefit is satisfied when it is proven that each active ingredient has made a meaningful contribution to the overall effect (safety and/or efficacy) of the combination.
There should not be any adverse interaction between the active ingredients (e.g. in the case of pharmaceutical incompatibilities or in case an active ingredient masks toxic effects of the other ingredients).

2.10.1 **Products containing Glucosamine and Chondroitin**

a) Products containing Glucosamine as single active ingredient are registrable as non-prescription product with indication as 'Adjuvant therapy for osteoarthritis'. Products containing Glucosamine in combination with Chondroitin are also registrable as non-prescription product with similar indication. Products containing Glucosamine either as single ingredient or in combination with other supplement ingredients are not allowed to be registered as dietary supplements.

b) Products containing Chondroitin either as single ingredient or in combination with other supplement ingredients will remain as dietary supplements whereby therapeutic claims are not allowed. The applications for registration are to be submitted as dietary supplements.

3. PROCEDURE FOR PROCESSING APPLICATIONS

3.1 Application Type

An application for a product registration may be sub-divided into one of the following:

(i) Application for an innovator product/new chemical entity

- containing a new chemical entity;
- containing a new combination of existing chemical entity(s);
- containing existing chemical entity(s) for use by a different route of administration;

(ii) Application for a generic[1] product (products containing Scheduled Poisons & products not containing Scheduled Poisons, including dietary/health supplements and herbal preparations)

[1 a generic product is a product that is essentially similar to a so called reference product/innovator product.]

3.2 Data Requirements

The data required to support an application is divided into:

a) Administrative documentation (Part I);

b) Quality documentation (Part II);

c) Safety and residues documentation (Part III); and

d) Efficacy documentation (Part IV).

Data to be submitted will be based on each application type as follows:

Innovator product – Parts I to IV

Generic product – Parts I & II

Applicants are advised to read the explanatory notes in ***Section 2*** of this registration guideline, and also the relevant ASEAN or VICH guidelines, for full information on product data requirement. In order to facilitate the evaluation process, applicants should conform to these guidelines. The DCA may in certain cases request for supplementary information. The applicant should make available the requested information within the specified period. Failure to do so may result in the rejection of the application for product registration.

4. APPLICATION FORMALITIES

The DCA accepts only web-based **online submissions** via **http://www.bpfk.gov.my.**

The applicant for product registration must be a locally incorporated company with a permanent address.

The applicant (if said company is not the product owner) should be authorized in writing by the product owner to be the holder of the product registration certificate and be responsible for all matters pertaining to the registration of the product.

4.1 Responsibility of Marketing Authorisation Holder (i.e. the applicant for product registration)

4.1.1 The applicant shall be responsible for the product and all information supplied in support of his application for registration of the product.

He shall be responsible for updating any information relevant to the product/application. The DCA should be informed in a timely manner any change in product information during the course of evaluation, and after product registration, especially if the information pertains to rejection/withdrawal, additional data on product efficacy and safety or current Good Manufacturing Practice (cGMP) compliance of the manufacturers (and repackers, if applicable).

4.1.2 Any person who knowingly supplies any false or misleading information in connection with his application for registration commits an offence under the Control of Drugs and Cosmetics Regulations 1984**. [Reg. 8(9)]**

4.1.3 The marketing authorisation holder must assume responsibility for the quality, safety and efficacy of his products.

4.2 Application Fee

4.2.1 Processing fee

Every application for registration shall be accompanied with a processing fee. The amount of fees is as stipulated in **The Control of Drugs and Cosmetics (Amendment) Regulations 2002**.

4.2.2 Other charges

The DCA will charge any applicant such costs it may incur for the purpose of carrying out any evaluation or investigation relating to the registration of any product. **[Reg. 8(3)]**

Any payment made is **not** refundable once an application has been submitted and payment confirmed. Applications without the correct fees will not be processed. **[Reg. 8(4)]**

4.3 Letter of Authorisation and Certification Which Must Accompany Applications

Letters of authorisation and certifications should be valid and current at the time of submission.

4.3.1 **All applications** for registration must be accompanied with the following:

(i) Letter of authorisation from the product owner. (NOT APPLICABLE IF THE APPLICANT IS THE PRODUCT OWNER);

(ii) Where a product is contract manufactured, letters of authorisation of contract manufacture and acceptance to and from the manufacturer and also each sub-contractor, if applicable (e.g. repacker).

The letter of authorisation should 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 letter of acceptance from the manufacturer shall comply with similar requirements as stated above.

The letters of authorisation and acceptance should 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.

4.3.2. **Imported products** will also need to furnish either a

(i) Certificate of Pharmaceutical Product (CPP) from the competent authority in the country of origin[2]; ***OR***

(ii) Certification for Free Sale (CFS) and Good Manufacturing Practice (GMP)[3] from the relevant competent authorities as deemed acceptable by the DCA.

CPPs shall be in the format of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce if issued by the Health Authorities listed in the WHO Certification Scheme (*list available from the WHO website*: http://www.who.int).

CPPs issued by EMEA for products registered through the centralized procedure in EU will be accepted.

CPPs 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 should be available for all the manufacturers.

The Drug Control Authority reserves the right to conduct an inspection on any manufacturing site.

[[2] In the event a CPP is not available from the country of 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 Licence for the manufacturer from the relevant competent authority, together with

(1) CPP from the country of the product owner; OR

(2) CPP from country of release, if (1) is not available]

[[3] DCA will usually recognize GMP Certification/Manufacturing Licence issued by the relevant national or regional Veterinary

Service or Department of Animal Health or Department of Agriculture.

In the event that a manufacturer is inspected by non-government body where GMP is voluntary but not obligatory under law, the issuing body must be officially recognized. A formal justification from the relevant national or regional Veterinary Service or Department of Animal Health or Department of Agriculture will need to be provided.

In the event that a manufacturer do not have GMP Certification/Manufacturing Licence due to not obligatory under law, FAMI-QS certification issued by officially recognized body is acceptable in Dietary/Health Supplement Product and Herbal/Natural Product. A formal justification from the relevant national or regional Veterinary Service or Department of Animal Health or Department of Agriculture will need to be provided.]

4.4 Multiple Applications

4.4.1 A separate application is required for each product i.e. products containing the same ingredients but made to different specifications (in terms of strength/content of ingredient(s), dosage form, description, etc.) or by a different manufacturer shall require separate applications for product registration.

Note: Different packings (materials) or pack sizes (quantity/volume) of a product (including parenteral preparations, and other solutions which are introduced into the bodies of animals) made by the same manufacturer to the same specifications, formulation and dosage form, 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.

4.4.2 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.

4.4.3 Proprietary products manufactured under licence by different manufacturers, or different subsidiaries, or in different countries under the same parent firm shall require separate registration.

5. PROCESSING OF APPLICATIONS

5.1 Initiation of Review

Review of applications will follow a queue system. There will be separate queues for the different categories of products

- NCE/innovator
- Generics

Priority review may be granted where the product 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).

5.2 Stop Clock

The clock starts once payment has been confirmed for a submitted application and will stop whenever the DCA needs to seek further information from the applicant. The clock restarts when the DCA receives complete responses from the applicant. A period of 6 **months** will be given within which the applicant should submit the additional information/clarification required for each correspondence from the DCA.

The clock stops when the DCA informs the applicant of its regulatory decision.

An application will be closed if the stop-clock (i.e. the time taken by the applicant to respond to enquiries) exceeds the 6 months given, and a new application will need to be submitted if the applicant wishes to pursue registration for the product in question.

The time-frame for registration for all categories of products **excludes** stop-clock time.

6. REGULATORY OUTCOME

6.1 Decisions of the DCA

A regulatory decision is made based on the outcome of the evaluation of the submitted documentation. An application may be approved or rejected and the DCA decision will be sent via e-mail to the marketing authorisation holder. Applicants are required to comply with the directions of the DCA *within the stipulated time* as stated in the DCA notification.

6.2 Product Registration Number [Reg. 8(8)]

A registration number will be given when a product application is deemed to have satisfied the registration requirements of quality, safety and efficacy and is granted **registration approval** by the DCA. The registration number is specific for the product registered with the name, identity, composition, characteristics, origin (manufacturer) and marketing authorisation holder as specified in the registration documents. It may NOT be used for any other product.

The marketing authorisation holder (i.e. applicant for product registration) will be notified of the DCA decision and given the product registration number assigned via e-mail immediately after each DCA meeting.

6.3 Rejection, Suspension or Cancellation of Registration [Reg. 11]

The DCA may reject, suspend or cancel 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.
Such products may not be imported, manufactured, sold, supplied, possessed for sale or administered.

6.4 Appeal Against DCA Decisions [Reg. 18]

6.4.1 Any applicant/marketing authorisation holder aggrieved by the decisions of the DCA may make a written appeal to the Minister of Health. **All notice of appeals MUST** be made within **fourteen (14) days** from the date of the DCA notification.

6.4.2 A period of 180 days from the date of notice of appeal is given for submission of any supporting data or documents for innovator products/NCE. A period of 90 days is allowed for other products. The appeal is considered closed if all the required information is not submitted within the stated time given. **Any request for extension of this period will not be entertained.**

6.5 Decision Of The Minister [Reg. 18]

The decision of the Minister made on any appeal is final.

7. MAINTENANCE OF REGISTRATION

7.1 Conditions For Registration [Reg. 8(1)]

The DCA may specify certain special conditions for registration for a particular product or group of products, and may amend any conditions for registration.

Specific product labeling requirements, for label and/or package insert, may also be laid down.

The DCA may cancel the registration of any product if the conditions for registration are not complied with.

7.2 Validity Period of Registration [Reg. 8(6)]

The registration of a product shall be valid for **5 years** or such period as specified by the DCA (unless sooner suspended or cancelled by the DCA).

Renewal of product registration can be done **six (6) months prior to the expiry** of the validity period of product registration. Upon expiry of the validity period of registration, the module for renewal of product registration will no longer be accessible and application for re-registration of the product can no longer be submitted.

8. CHANGE IN PARTICULARS OF REGISTERED PRODUCTS

8.1 No change in product name, product specifications, packing, indications, contents of product label, package insert, or product literature, or any relevant particulars of the registered product shall be made without the prior approval of the DCA.

Similarly, prior approval of the DCA is required for changes in excipients, such as change in lubricant, preservative, solvent in film coating, etc to improve product formulation.

Explanation/reason for the changes requested should be given. All relevant supporting data related to the above changes such as finished product quality specifications (FPQC), Certificates of Analysis (CA), stability data, raw material specifications, etc should be updated accordingly.

The registration of a product may be cancelled if changes are made without the prior approval of the DCA.

8.2 All necessary documents in accordance to the specified conditions laid down for each type of variation (amendment) should be submitted. The marketing authorisation holder is responsible for ensuring that all the necessary validation has been conducted to demonstrate that the change does not reduce the quality, safety or efficacy of the product. (Please refer **Appendix 2** for details of the types of variations allowed and the conditions and/or supporting documents necessary for each type of variation defined.)

8.3 Any change which affects the composition or characteristics of the product such as **colour/shade, flavour/fragrance, shape, change of vehicle** (liquid preparation) shall require a new application for registration.

9. REPORTING PROBLEMS WITH REGISTERED PRODUCTS

9.1 Adverse Drug Reactions

The Malaysian Veterinary Adverse Drug Reactions Advisory Committee (MVADRAC), Sub-committee of the Drug Control Authority (DCA), reviews Malaysian reports of suspected drug reactions.

9.1.1 MVADRAC encourages animal health care professionals, farmers, public and other users of veterinary medicines to report all suspected adverse reactions but it is a compulsory requirement that the marketing authorisation holder of a product should inform the DCA of any adverse reactions to the target animal, non-target animal and to the person handling the product.

9.1.2 The product registration can be cancelled if the marketing authorisation holder fails to inform the DCA of any serious adverse reactions upon receipt of such reports.

9.1.3 All labels and package inserts must be amended to include any new adverse reactions, warning, precautions etc. within the time frame given by the DCA.

9.2 Market Surveillance of registered products

9.2.1 Samples of products registered by the DCA may be taken and tested for compliance with official or pharmacopoeia standards or specifications agreed by the manufacturer.

9.2.2 If a sample fails to meet adequate specifications, the marketing authorisation holder will be issued a warning. Unless the failure is serious enough to justify recall of the product, the marketing authorisation holder has up to 30 days to identify the

source/cause of quality defect and actions to be taken to improve quality.

9.3 **Product Complaints**

9.3.1 The marketing authorisation holder should notify the DCA of any product quality related problems (with registered products) that the holder is aware of.

9.3.2 It is also the responsibility of the prescribers, the pharmacists, as well as all other animal health professionals who come into contact with the drug to report.

9.4 **Product Recalls**

9.4.1 Recalls of defective or unsafe products are instituted by the DCA, supported by the Pharmaceutical Services Division, Ministry of Health Malaysia.

9.4.2 The marketing authorisation holder is responsible for conducting recalls of defective or unsafe products. No recall should take place without first consulting/informing the DCA.

10. TERMINATION OF PRODUCT REGISTRATION BY MARKETING AUTHORISATION HOLDER

10.1 The marketing authorisation holder shall inform the DCA of any decision to terminate the registration of a product before the end of the validity of such registration. The onus is on the holder to inform the manufacturer/contract giver.

10.2 The marketing authorisation holder must surrender the product registration certificate immediately to the DCA.

10.3 The registration of a product once terminated shall not be reinstated. A new application must be submitted should its registration be required again at a later date.

11. CHANGE IN MARKETING AUTHORISATION HOLDER OF A REGISTERED PRODUCT

Please refer to **Appendix 3** for **Guide to transfer of product marketing authorisations.**

12 CHANGE IN MANUFACTURING SITE

12.1 Applies to change of manufacturing site for part or all of the manufacturing process of the product but does not cover changes related to a new site where only batch release takes place or 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).
The new manufacturing site should comply to current Good Manufacturing Practice. Local manufacturing sites are subjected to pre-licensing inspections and for manufacturing sites outside Malaysia, certification by the competent authority is sufficient. However, the **DCA reserves the right to conduct an inspection on any manufacturing site**.

12.2 This procedure is only applicable for:

a) a change in manufacturing site for the same company, including rationalization in the event of mergers; and

b) where 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 below).

12.3 There are 5 different types of site change, according to different scenarios and hence require different sets of accompanying documents.

Type 1 : Change of manufacturing site within Malaysia

Type 1 is 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. The equipment, standard operating procedure (SOP's), environmental conditions (e.g. temperature and humidity) and controls remain the same.

Type II : Change of manufacturing site from foreign country to Malaysia

Type II is 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. The equipment, standard operating procedure (SOP's), environmental conditions (e.g. temperature and humidity) and controls remain the same.

Type III : Change to manufacturing site located outside Malaysia.

Type III is a 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.

Type IV : Change of manufacturing site for special category of products.

Type IV is a change of location of the site of manufacture for the following categories of products.

1) Products consisting of allergens, blood products and products derived from biotechnology.

2) Transfer of manufacturing of an aseptically processed sterile product to a (i) newly constructed or refurbished aseptic processing facility or area or (ii) 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 no approved lyophilized products are manufactured).

3) Transfer of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site. Once this change has been approved, subsequent site changes to the facility for similar product types and processes will not be categorized as a Type IV.

Type V : Crisis Situation

Type V is a change of location of the site of manufacturer that is deemed necessary due to certain circumstances such as natural disasters, closure or suspension of premise (revocation of manufacturing licence) and matters related to breach of product quality, safety and efficacy. There may be instances where Type V change may involve a new manufacturer.

Types II, III, IV and V require change of manufacturing site application.

(Please refer **Appendix 4** for details of documentation to be supplied with each type of site change**)**.

13. OTHER INFORMATION

13.1 Criteria for registration

A product will be registered only if it satisfies **ALL** requirements of the DCA, especially **with respect to safety, efficacy and quality** of the product.

Other criteria that may be taken into consideration include:

(i) Either that the product is needed or not. Aspects like potential for abuse, number of registered products, different dosage form, etc are considered;

(ii) Therapeutic advantage.

13.2 Brand/Proprietary Name

The DCA will register product with specific brand/proprietary name for only one Marketing Authorisation Holder.
The same brand/proprietary name is not allowed for other marketing authorisation holder.

13.3 Variants for a Given Product

Applications for variants (different colour/flavours) for veterinary products will be considered on a case by case basis.

13.4 Products for export only

13.4.1 The DCA may register the following locally manufactured **Scheduled Poison** products for export only:

- Poduct(s) registered by the DCA but sold in a different colour (formulation), shape and strength;
- Product(s) which contain ingredients not allowed by the DCA for local use, **provided that** confirmation in writing is obtained from the competent authority of the importing country that there is no objection to the importation and sale of the formulation in question. Evidence of registration of said formulation with the competent authority in importing country may be accepted as supporting data.

13.4.2 For products **other than Scheduled Poison** locally manufactured for export only shall be notified through the notification procedure. In this case notification number will be given to the respective products.

13.4.3 Registration of product for export purposes is not necessary if there is no change in the formulation or appearance of the product. An "export notification" procedure allows an applicant to apply for free sale certification for the product whereby the applicant need only declare to the DCA the differences in the product for export compared to the registered product marketed in Malaysia (such as a product being exported under a different name).

A Certificate of a Pharmaceutical Product will be issued to the applicant for the registered product together with an explanation of any difference(s) to the importing country.

13.5 Bioequivalence

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, will be established by the DCA.

13.6 New/additional indication

New/additional indication is defined as an indication which is not previously approved for a registered product. This includes a new therapeutic indication and does not include changing/rephrasing of sentence

13.7 Protocol of Analysis

The Protocol of Analysis for a product is a requirement for the registration of the product and must be submitted with the initial data submission for product registration. This protocol of analysis must be in the manufacturer's official format and must comply with NPCB's requirements as mentioned in Annex A. Evaluation of the protocol of analysis will be conducted together with the analysis of the product after the said product is registered. The onus is on the applicant to ensure that the testing methods in the protocol of analysis are validated and suitable under actual conditions of use. If the protocol of

analysis is found to be unsatisfactory or unavailable or if the test method submitted in the protocol is not reproducible/workable, action will be taken to cancel the registration of the said product.

Analytical method validation data can be submitted if available. This data must comply with the requirements of the relevant International/ASEAN guidelines for analytical method validation.

This requirement is not applicable to the herbal preparations.

14. TYPES OF APPLICATIONS

- Product registration
- Renewal of product registration.
- Change in manufacturing site
- Change in Marketing Authorisation Holder
- New/additional indication
- Amendments to particulars of a registered product (variation)
- Product registration for export only.
- Appeals against DCA decision
- Withdrawal (of a product registration application prior to its approval)
- Termination (of product registration)

15. APPENDICES

Appendix 1:	General Conditions for Registration of Drug Products under the **Control of Drugs and Cosmetics Regulations 1984** **Appendix 1.1 :** Product Identification Chart - for security device labelling
Appendix 2:	Guidelines on Application for Variation Of Registered Products
Appendix 3:	Guide To Transfer Of Product Marketing Authorisations
Appendix 4:	Supporting Documentation required for Change in Manufacturing Site Application
Appendix 5:	Permitted colouring agents in pharmaceutical and traditional products
Appendix 6:	Ingredient that affect the characteristic of feed

Appendix 7:	Exemption list as single ingredient on vitamins, amino acids, minerals, electrolytes & others for manufacturing purpose only
Appendix 8:	Indication and functional claims for Health/Dietary Supplement Product
Appendix 9:	List Of Prohibited Botanicals (Herbs and Herbal Derivatives)
Appendix 10:	List of ingredients (active) not allowed to be registered by the Drug Control Authority
Appendix 11:	Guideline for Stability Data
Appendix 12:	Allowable Maximum Residual Limit (MRL)
Appendix 13:	Classification of Ingredients for Veterinary Use
Appendix 14 :	Regulation of Veterinary Products in Malaysia

APPENDIX 1 : GENERAL CONDITIONS FOR REGISTRATION OF DRUG PRODUCTS UNDER THE CONTROL OF DRUGS AND COSMETICS REGULATIONS, 1984

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.

2. Product Particulars:

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

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

3. Labelling :

   The registered product shall be labelled with the Registration Number.

   The labels for the registered product shall comply with all other labelling requirements specified by the DCA.

4. Product authentication :

   The registered product shall be affixed with the security device approved by the DCA. The said security device, which is serialized, shall be used to authenticate and verify that the product is registered with the DCA, 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 **Appendix 1.1** for Product Identification Chart which indicates where the security device may be affixed on the product label*)

5. Indications, Special Conditions:

   The registered product shall only be indicated for use as approved by the DCA.

The importation, manufacture, sale and supply of the registered product shall comply with all other specific conditions imposed by the DCA.

6. Adverse Reactions, Complaints:

   The holder of the registration certificate shall inform the DCA of any adverse reactions of or complaints on the registered product immediately after he receives notice of such adverse reactions or complaints.

7. Holder of Registration Certificate:

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

8. Withdrawal From Registration :

   The holder of the registration certificate shall notify the DCA of any decision to withdraw the registration of the product and shall state the reasons for the decision.

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

9. Cancellation, Suspension, Amendment by DCA :

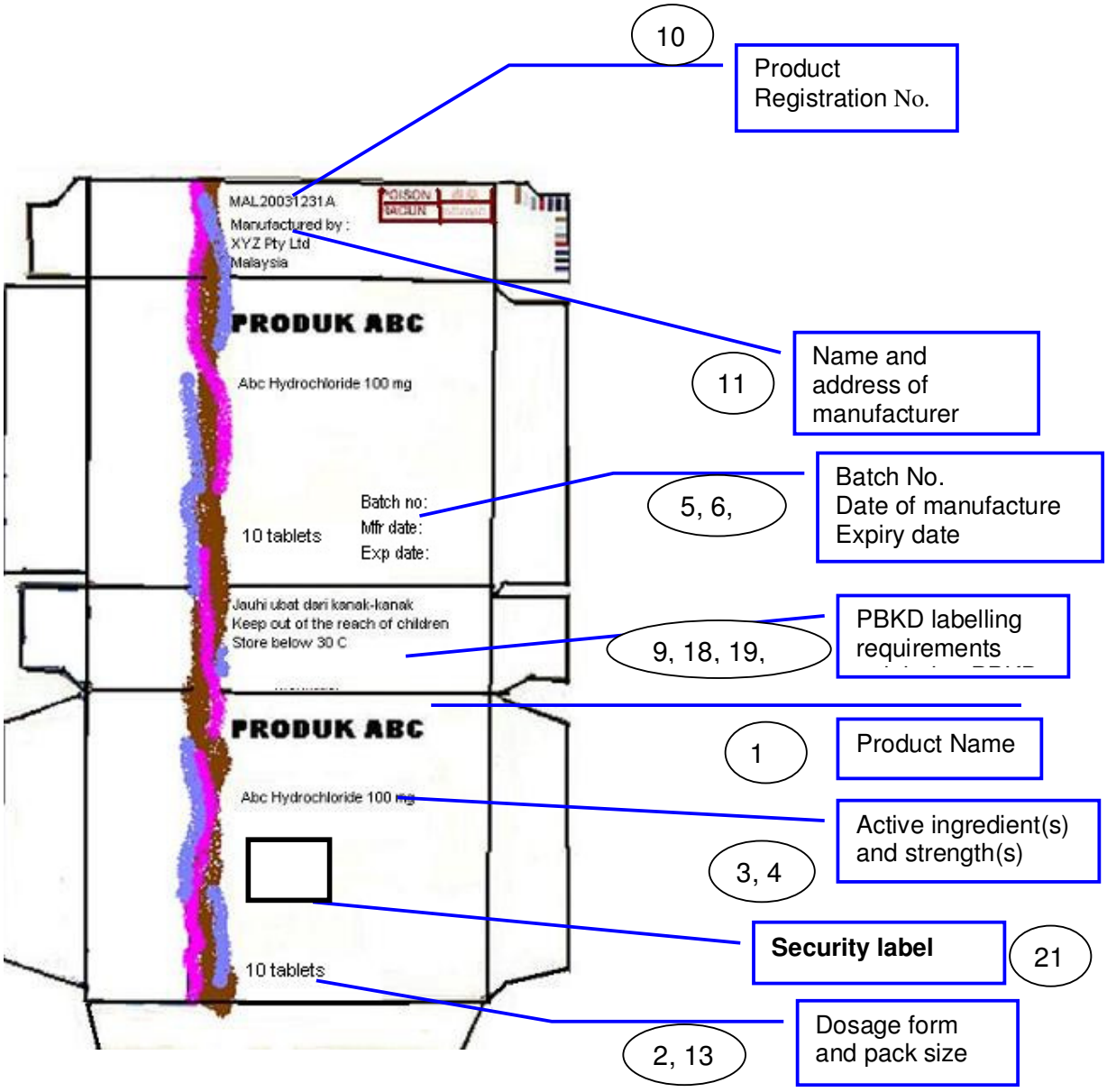
   The DCA may, at any time and without assigning any reason suspend or cancel the registration of any product, and may amend the conditions to which such registration is subject.

   The holder of the registration certificate shall immediately surrender to the DCA the registration certificate upon cancellation or suspension of the registration of the product.

10. DCA Directions :

    The holder of the registration certificate shall comply with any directions issued by the DCA for the better carrying out of the provisions of these Regulations.

APPENDIX 1.1 : PRODUCT IDENTIFICATION CHART (to identify where the security device may be affixed on the product label)



Numerical notation in line with the numbering for the parameters to be included in the product label as stated in Section D.

APPENDIX 2 : GUIDELINES ON APPLICATION FOR VARIATION OF REGISTERED PRODUCTS

The purpose of this guidelines is to provide guidance to marketing authorization holders (MAH)/applicants who intend to apply to vary the registered information of a registered product. The guideline defines the type of variations and outlines the supporting documents necessary for each type of variation:

Type I: Minor variation with a 14 days validation period

> The marketing authorization holder may proceed to implement the change after a 14 days validation period upon the date of receiving the documents by variation unit.
> Minor variations are subject to the conditions specified.

FOR INTERIM PERIOD:

An applicant may submit Type I variation manually together with the required documents by using the form specified. The manual submission must be submitted together with variation online application. The approval will only be notified via online submission.

Type II: Major Variation

> Type II variation is considered a major change and approval is required prior to implementation.

The Marketing Authorization Holder is responsible for ensuring that all the necessary validation has been conducted to demonstrate that the change does not reduce the quality, safety or efficacy of the product.

ATTACHMENT 1

TYPE I

No.	TITLE OF VARIATION	AFFECTED FIELDS PHARMACEUTICAL	SUPPORTING DOCUMENTS REQUIRED OR CONDITIONS TO BE FULFILLED
1.	Change in name of manufacturer and/or repacker without any change in address of site.	Can be made through **VIEW & EDIT VALIDATION**	a) Certificate of name change i.e. Form 13 Company Act 1965. → please attach the supporting document at **E12**.
2.	Change in company logo on the packaging components (without any changes on graphic or label content)	D1, D2, D3	a) Draft packaging components with the amended information.
3.	Change in importer or distributor	E13.1	
4.	Replacement, 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.	A4, P1, P5.1, P5.2 , D3, E8(if applicable**)**	a) Finished product release and shelf life specification have not been changed except for the description b) Any new ink must comply with the relevant pharmaceutical legislation. - New description of the product.
5.	Change in shape or dimensions of the container or closure.	P7	a) No change in the type of container or closure. b) The product is not intended to be sterile. c) No change is made to the product shelf life and/or storage conditions.
6.	Change in pack size of the finished product. Change in the number or units (e.g. tablets, ampoules) in a pack. Change in volume of non sterile preparations. Change in volume of parenteral preparations and peritoneal dialysis with similar characteristics.	C1, D3, E8(if applicable)	a) The primary packaging materials remains the same.

7.	Tightening of specification limits of finished product or active ingredient.	E9,E10 P5.1, P5.2,P 5.4 S4.1, S4.2,S 4.4	a) New specifications b) **Certificate of analysis (CoA) FPQC (P5.4) or active ingredient X 1 batch (S4.4)**
8.	Change in source or addition of source of active ingredient **without any change in specification** (except direct compressed granules/ pellets).	S2.1	a) Finished product release and end of shelf life specification remains the same.
9.	Change in secondary packaging material	C2, D1, D2, D3 P7	a) The primary packaging material remains the same. b) Draft packaging components.
10.	Change in test procedure or analytical protocols of finished product.	E9, E10	a) Appropriate (re-)validation studies have been performed in accordance with relevant guidelines. b) Results of method validation show new test procedure to be at least equivalent to the former procedure. c) Finished product specifications are not adversely affected.
11.	Change in name and/or address of a manufacturer of the active substance	S2.1	
12.	Change in testing procedure of an excipient	P4.2, P4.3	Specifications of the excipient/finished product remain the same.

TYPE II

1.	Change in product name only.	Can be made through **VIEW & EDIT VALIDATION**	a) Draft label and leaflet. b) Letter confirming change in name only issued by the MAH or manufacturer.
2.	Change in content of leaflet or prescribing information/PIL/SPC.	A1 – A17, C1 D3, E7 (Summary of Product Characteristics from manufacturer) E8 (if applicable)	a) For all types of product provide:- - Copy with amendments clearly marked. - Clean copy of the proposed new leaflet. → please note that only clean copy of package insert is to be attached at D3 in addition to the supporting documents. b) Provide the following (innovator product only):- - Company Core Data sheet - Conclusion or abstract of recent Periodic Safety Update Report where relevant. - Expert Clinical Report (if applicable) For generic product please provide a copy of reference to support the change
3.	Change in content of label inclusive of change in graphics.	D1, D2	a) Draft label with changes marked clearly. b) Clean copy of label
4.	Change in manufacturing process of the finished product	E11, P 3.2, P3.2.1, P3.3, P3.4, P5.1, P 5.4, P8	a) Finished product specification is not adversely affected. b) The new process must lead to an identical product regarding all aspect of quality, safety and efficacy. c) The product does not contain a biological active substance. ⊕ **Certificate of analysis (CoA) FPQC (P5.4)** - **Requirement :** **2 batches for imported products** **1 batch for locally manufactured products**
5.	Change in **overage of active ingredient or excipient**	B1.1, B1.2	Finished product release and end of shelf life specification remains the same
6.	Replacement of an excipient with a comparable excipient and/or change in content of excipient. (Excluding colouring and or flavouring agent).	Can be made through **VIEW & EDIT VALIDATION**	a) No changes on the specification of the excipient for product specific requirements (e.g. particle size profiles, polymorphic form, etc.), if applicable. b) Any new excipient does not include the use of materials of human or animal origin for which assessment is required of viral safety data. c) Provide the following:- 1. Comparison of new and existing formula 2. Batch Manufacturing Formula 3. Excipient specification 4. Manufacturing process 5. Stability data of finished product (refer to Malaysian Guidelines for Stability Studies of Drug Product for data required) -} new formula

			6. To amend label (If applicable, i.e. if the variations involve the addition of preservative /alcohol) (D1 & D2) 7. Certificate of analysis (CoA) FPQC X 1 batch (P5.4) } of the new formula
7.	Change in batch size.	B 1.1, B1.2	a) The change does not affect the reproducibility and/or consistency of the product. b) No change to the manufacturing method nor to the in-process controls other that those necessitated by the change in batch-size, e.g. use of different size equipment. c) Finished product specification is not adversely affected. d) To provide Batch manufacturing formula e) batch comparative analysis - imported product/s : 3 batch for each old and new batch size - locally manufactured product/s: 3 batch for old and 1 new batch → to attach the batch analysis at P5.4
8.	Change in capsule shell or film coated agent.	Can be made through **VIEW & EDIT VALIDATION**	a) Includes change of hard gelatin capsule to vegetable capsule but does not apply change from hard gelatin capsule to soft gel capsule. b) Provide the following :- - New unit formula for coating agent - Batch manufacturing formula - New manufacturing process c) Stability data of finished product (refer to Malaysian Guidelines for Stability Studies of Drug Product for data required) d) To include the function for each and every excipient used.
9.	Change in finished product or active ingredient specification	E9, E10, P5.1, S4.1	a) Includes addition of a new test parameter. Certificate of analysis for one batch (for locally manufactured product/s) or two batches (for imported product/s) as per the new specification to be provided upon approval and when change is affected.
10.	Change to in-process tests or limits applied during manufacture of the product.	P3.3	a) Includes tightening of in-process limits and addition of new tests b) Any change should be within the range of the currently approved limits.
11.	Change/ addition in primary packaging material.	C2, D1, D2, D3 P3.2, P8	a) Provide the following:- - Assembly process for the new packaging material - Stability data (refer to Malaysian Guidelines for Stability Studies of Drug Product for data required) - Draft label
12.	Change in shelf life of finished product:- As packaged for sale After first opening After reconstitution	A15, A16, P8 D1,D2, D3	a) Provide stability data (refer to Malaysian Guidelines for Stability Studies of Drug Product for data required)

13.	Change in storage conditions	A15, P8 D1,D2, D3	a) Provide stability data (refer to Malaysian Guidelines for Stability Studies of Drug Product for data required)
14.	Appointment or change in repacker.	D1, D2, D3 , E14, *E12 (for other supportive documents)	a) Provide the following:- - *GMP certificate of the new packer - *Assembling process - ***Letter of appointment and acceptance for contract repacker** - Draft label
15.	Change in target species	A6.2	a) Addition of a non-food producing species:- - Pharmacokinetics and metabolism in target species, or comment on adequacy of the justification for not providing such data - Efficacy in the additional target species - Tolerance in the additional target species - Likely increase in operator exposure - Likely increase in environmental load or pattern of exposure b) Extension to include new target group (subset of target species):- - Pharmacokinetics and metabolism in target group, or comment on adequacy of the justification for not providing such data - Efficacy in the new target group - Tolerance in the new target group - Likely increase in operator exposure - Relevance of original residue studies and stability of existing withdrawal periods in the case of food producing species - Change to environmental load
16.	Change in withdrawal period	A18.1	Provide safety and residues data which are supported by evidence
17.	Change in maximum residual limit (MRL)	A18.2	Provide safety and residues data which are supported by evidence

NOTE:

1. **Other supportive documents can be attached at E12 where such documents are necessary.**

2. **Please note that for every variations made, reason for changing/remarks should be clearly written and explained.**

3. **Please note that there will be no correspondence with the applicant for variation module. For any rejection made for 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 must be submitted.**

APPENDIX 3 : GUIDE TO TRANSFER OF PRODUCT MARKETING AUTHORISATIONS

INTRODUCTION

A product registration (marketing authorisation) may be transferred from the existing product marketing authorisation holder (MAH) to another holder using a transfer procedure. This administrative procedure allows for a speedy processing time and the same product registration number is maintained.

The transfer procedure must be used where the legal entity of the MAH is changed.

CONDITONS

In order to avail of this procedure, the following requirements must be met:

1. An application for permission to transfer the marketing authorisation of a product should be submitted by the proposed new MAH.

2. The existing product registration must have a remaining period of validity of at least six (6) months. If the period is less than six (6) months, product registration renewal should be done by the existing MAH before the transfer application is submitted.

3. No change may be made, as part of the transfer application, to the technical data or approved pharmaceutical/pharmacological information, including the texts of the product label and leaflet, other than the name and address of the MAH.
   [Note: any change must be applied for using the variations procedure.]

4. The transferred marketing authorisation is issued for the remaining period of validity of the existing authorisation.

5. The transfer shall come into effect on the day the DCA makes its decision on the application. Upon the transfer of product registration (marketing authorisation) to the new holder, the authorisation issued to the previous holder will be cancelled as the product cannot be marketed simultaneously by two different MAHs. The new i.e. current MAH shall bear responsibility for the product.

6. Where the application does not meet the requirements laid down for this administrative transfer procedure or

the applicant wishes to obtain a new product registration number, a new application shall be made.

MAKING AN APPLICATION

The proposed new MAH must submit an application consisting of the following:

- Processing fee for the transfer application (nonrefundable).

- Transfer application form :
  - on-line (change of registration holder tray)

- A copy of the agreement concluded between the current MAH, the proposed new holder and the product owner to the mutual transfer of the product marketing authorisation (***preferably***),

  OR alternatively**,**

  Signed statements[1] relating to transfer of authorisation from
  - existing product registration holder
  - proposed new holder
  - product owner.

- Current confirmation letters (from product owner and contract manufacturer) relating to agreement for contract manufacturing, where applicable.

- Latest product label and leaflet.

[*Note **1** - Examples of the statements that can be used are given as :*
Transfer Form 430.5(1) *(statement to be signed by existing holder), &*
Transfer Form 430.5(2) *(statement to be signed by proposed new holder).* **]**

TRANSFER FORM 430.5(1)

STATEMENT TO BE SIGNED BY THE EXISTING PRODUCT MARKETING AUTHORISATION (REGISTRATION) HOLDER

Reason for transfer application:

1. I hereby notify the Drug Control Authority (DCA) Ministry of Health Malaysia, that

   ……..(Name of product)
   ……..(Registration Number of product)
   is to be transferred to
   ……..(name of proposed new MAH).

2. I confirm also that the entire dossier for the product is transferred to ……. (name of new proposed MAH).

   This dossier includes all the data in support of the original application together with all correspondence with the DCA/National Pharmaceutical Control Bureau concerning the product .

   Signed :

   Full name :

   Identity Card Number:

   Status of signatory *:

   Official Company stamp:

   Telephone Number:

   Fax Number:

   Date :

   * To be signed by the Managing Director/President/CEO or an equivalent person who has overall responsibility for the company or organisation.

TRANSFER FORM 430.5(2)

STATEMENT TO BE SIGNED BY THE PROPOSED NEW PRODUCT MARKETING AUTHORISATION (REGISTRATION) HOLDER

Reason for transfer application:

1. I have received/accepted the entire dossier for
   ……..(Name of product)
   ……..(Registration Number of product)
   from ……(Name of existing MAH).).

   This dossier includes all the data in support of the original application together with all correspondence with the DCA/National Pharmaceutical Control Bureau concerning the product.

2. I hereby agree that I have sole responsibility for the product including obtaining approval for any subsequent product variation and maintenance of product registration.

3. I also acknowledge responsibility in the event of pharmacovigilance issues or quality defects associated with the product that may occur in the interim transfer period.

   Signed :

   Full name :

   Identity Card Number:

   Status of signatory *:

   Official Company stamp:

   Telephone Number:

   Fax Number:

   Date :

   * To be signed by the Managing Director/President/CEO or an equivalent person who has overall responsibility for the company or organisation.

APPENDIX 4. : SUPPORTING DOCUMENTS WHICH NEED TO BE SUBMITTED FOR CHANGE IN MANUFACTURING SITE APPLICATION

No	Document to be submitted	Type II	Type III	TypeIII IV	Type V
1.	Letter of authorisation/appointment from the manufacturer/product owner	√	√	√	√
2.	Letter from the manufacturer/product owner to clarify/explain the need to change site of manufacture	√	√	√	√
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 OR If there are minor changes, to declare the 'minor changes' & justify the need for such changes.	√	√	√	√
4.	'Release' and 'end-of-life' specifications as approved by the DCA	√	√	√	√
5.	Original copy of the Certificate of Free Sale and Good Manufacturing Practice/ Certificate of Pharmaceutical Product from the source country of the new manufacturing site in the case of an imported product or confirmation of GMP status (according to Guideline) for a locally manufactured product.	√	√	√	√
6.	Original copy of Certificate of Analysis for I batch of product from the new manufacturing site	√	√	√	
7.	"Accelerated" stability data for at least 3 months for 1 batch of product manufactured at the new site. (3 months at 45-50ºC and RH 75%, 6 months at 40ºC and RH 75%)	√	√	√	
8.	Amended immediate label, outer label and package insert for the product from the new site	√	√	√	√
9.	Process Validation Report for the new site for 3 batches (pilot or commercial scale) **OR** Process Validation Report for the pilot scale together with a confirmation from the manufacturer that complete process validation will be carried out on 3 following consecutive batches **OR** Retrospective Validation Report (Refer Guideline)		√	√	
10.	Commitment to submit long term stability data	√	√	√	
11.	Commitment to submit stability data, certificate of analysis 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.	√		√	

APPENDIX 5 : PERMITTED COLOURING AGENTS IN DRUG PRODUCTS

NO.	COLOURANT
1.	Allura Red AC
2.	Anthocyanins a. Those glycosides of 2-phenylbenzopyrylium salts which are anthocyanins b. The following anthocyanidin aglycones : - Pelargonidin - Cyanidin - Peonidin - Delphinidin - Petunidin - Malvidin
3.	Beetroot Red, Betanin (Aqueous extracts)
4.	Black PN (Brilliant Black BN)
5.	Brilliant Blue FCF
6.	Calcium Carbonate
7.	Carbo medicinals/vegetalis; (charcoal)
8.	Caramel
9.	Carmoisine (or Azorubine)
10.	Carotenoids a. Alpha, Beta, Gamma-Carotene b. Bixin, Noribixin, Roucou, Annatto c. Capsanthin, Capsorubin, (paprika extract) d. Lycopene e. Beta-Apo-8' carotenal (C 30) f. Ethyl ester of Beta-Apo-8 Carotenoic Acid (C30). i. Chlorophyll ii. Copper complexes of Chlorophyll and Chlorophyllins
11.	Chocolate Brown HT
12.	Cochineal or Carminic acid, Carmine from Cochineal
13.	Curcumin
14.	Fast Green FCF (FD & C Green No.3)
15.	Green S (Acid Brilliant Green BS, Lissamine Green)
16.	Indigo Carmine (Indigotine)
17.	Lactoflavin, Riboflavin
18.	Orange Yellow S (Sunset Yellow FCF)
19.	Patent Blue V
20.	Ponceau 4R (Cochineal Red A)
21.	Quinoline Yellow

22.	Red 2G
23.	Xanthophylls a. Flavoxanthin b. Lutein c. Cryptoxanthin (Kryptoxanthin) d. Violoxanthin e. Rhodoxanthin f. Canthaxanthin
24.	The following colouring matters natural to edible fruits or vegetables :- Alkannin Annatto (including eye) Carotene (including eye) Chlorophyll Flavine Indigo Osage Orange Persian Berry Saf flower Saffron Sandalwood Tumeric or their pure colouring principles whether isolated from such natural colours or produced synthetically
25.	Bole or Iron oxide, Carbon Black (or vegetable origin), Titanium dioxide
26.	The Aluminium salts (lakes) of any of the scheduled synthetic dyes approved for use, (a) Alumina (Dried Aluminium Hydroxide)
27.	Dihydroxyacetone (external use with specific drugs only)
28.	Bismuth Oxychloride (external use only, including eye)
29.	Ferric Ammonium Ferrocyanide (external use only, including eye)
30.	Ferric Ferrocyanide (external eye only)
31.	Chromium Hydroxide Green (external use only)
32.	Chromium Oxide Green (external use only, including eye)
33.	Guanine (external use only)
34.	Prophyllite (external use only)
35.	Mica (external use only, including eye)
36.	Talc
37.	Bronze (external use only, including eye)
38.	Copper (external use only, including eye)
39.	Zinc Oxide (external use only, including eye)
40.	FD & Blue No. 2
41.	D & C Blue No. 4
42.	D & C Green No. 5
43.	D & C Green No. 6 (external use only)
44.	D & C Green No. 8 (external use only)
45.	D & C Orange No. 4 (external use only)
46.	D & C Orange No. 5 (mouth wash, dentifrices, external use only)

47.	D & C Orange No. 10 (external use only)
48.	D & C Orange No. 11 (external use only)
49.	FD & C Red No. 4 (external use only)
50.	D & C Red No. 6 – may be use in combination; total not more than 5mg/day
51.	D & C Red No. 7 – may be used in combination; total not more than 5mg/day
52.	D & C Red No. 17
53.	D & C Red No. 21
54.	D & C Red No. 22
55.	D & C Red No. 27
56.	D & C Red No. 28
57.	D & C Red No. 30
58.	D & C Red No. 31 (external use only)
59.	D & C Red No. 34 (external use only)
60.	D & C Red No. 39 (external use only, not more than 0.1%)
61.	D & C Yellow No. 7 (external use only)
62.	Ext. D & C Yellow No. 7 (external use only)
63.	D & C Yellow No. 8 (external use only)
64.	D & C Yellow No. 11 (external use only)
65.	Tartrazine/FD & C Yellow No. 5/MA Yellow A-2/Aluminic lake (external use only)
66.	Erythrosine/FD & C Red No. 3
67.	Yellow 2G (food yellow)
68.	D & C Yellow No. 6

APPENDIX 6 : INGREDIENTS THAT AFFECT THE CHARACTERISTIC OF FEED

A. ANTIOXIDANTS

1 5, 6-Diacetyl-L-ascorbic acid
2 6-Palmityl-L-ascorbic acid (ascorbyl palmitate)
3 Butylated hydroxyanisole (BHA)
4 Butylated hydroxytoluene (BHT)
5 Calcium L-ascorbate
6 Dodecyl gallate
7 Ethoxyquin
8 L-ascorbic acid
9 Octyl gallate
10 Phospholipids (including lecithin) from natural sources
11 Propyl gallate
12 Sodium L-ascorbate
13 Synthetic alpha-tocopherol
14 Synthetic delta tocopherol
15 Synthetic gamma-tocopherol
16 Tocopherol-rich extracts of natural origin

B COLOURANTS/PIGMENTERS AND MICROTRACERS

1 Acid Brilliant Green BS, (Lissamine Green)
2 All colouring agents permitted for colouring foodstuffs, being Colouring agents not otherwise specified in this Part, as described in the Food Standards Code
3 Astaxanthin
4 Beta-apo-8'-carotenal
5 Canthaxanthin
6 Capsanthin
7 Citranaxanthin
8 Cryptoxanthin
9 Ethyl ester of beta-apo-8'-carotenoic acid
10 Iron and stainless steel grit
11 Lutein
12 Patent Blue V
13 Zeaxanthin

C PRESERVATIVES AND MOULD INHIBITORS

1 3-p-cymenol
2 Acetic acid
3 Ammonium formate

4 Ammonium propionate
5 Benzalkonium chloride and related alkylaryl quaternary ammonium salts
6 Benzoic acid
7 Calcium acetate
8 Calcium citrate
9 Calcium formate
10 Calcium lactate
11 Calcium propionate
12 Calcium sorbate
13 Citric acid
14 Ethyl-4-hydroxybenzoate
15 Formalin
16 Formic acid
17 Fumaric acid
18 Hydrochloric acid
19 L-Tartaric acid
20 Lactic acid
21 Malic acid
22 Methyl-4-hydroxybenzoate
23 Methylpropionic acid
24 Orthophosphoric potassium acetate acid (phosphoric acid)
25 Potassium acetate
26 Potassium citrate
27 Potassium L-tartrate
28 Potassium lactate
29 Potassium propionate
30 Potassium sodium L-tartrate
31 Potassium sorbate
32 Propionic acid
33 Propyl-4-hydroxybenzoate
34 Propyl acetate
35 Propyl benzoate
36 Propylene glycol
37 Pyrolignous acid
38 Sodium bisulphite
39 Sodium citrate
40 Sodium diacetate
41 Sodium ethyl-4-hydroxybenzoate
42 Sodium formate
43 Sodium L-tartrate
44 Sodium lactate
45 Sodium meta-bisulphite
46 Sodium methyl-4-hydroxybenzoate
47 Sodium nitrite
48 Sodium propionate
49 Sodium propyl-4-hydroxybenzoate
50 Sodium sorbate
51 Sorbic acid
52 Sulphuric acid

D BINDERS, ANTI-CAKING AGENTS, COAGULANTS, FEED HANDLING IMPROVERS

1 Aluminium silicates, synthetic
2 Bentonite/montmorillonite
3 Calcium aluminates, synthetic
4 Calcium silicate, synthetic
5 Calcium sulphate and Calcium sulphate dihydrate
6 Carboxymethyl cellulose (sodium salt of carboxymethyl ether of cellulose)
7 Citric acid
8 Collagen
8 Diatomaceous earth
9 Kaolinitic clays, free of asbestos
10 Lignosulphonates
11 Molasses
12 Natural mixtures of steatite and chlorite
13 Perlite
14 Sepiolite
15 Silica (silicon dioxide)
16 Silica gel
17 Sodium aluminosilicate, synthetic
18 Sodium, potassium and calcium stearates
19 Urea formaldehyde resin
20 Vermiculite

E ACIDITY REGULATORS

1 Ammonium carbonate
2 Ammonium chloride
3 Ammonium dihydrogen orthophosphate
4 Ammonium hydrogen carbonate
5 Calcium carbonate
6 Calcium hydrogen orthophosphate
7 Calcium oxide
8 Calcium tetra-hydrogen diorthophosphate
9 Citric acid
10 di Ammonium hydrogen orthophosphate
11 di Calcium diphosphate
12 di Potassium dihydrogen orthophosphate
13 di Sodium dihydrogen diphosphate
14 di Sodium hydrogen orthophosphate
15 Hydrochloric acid
16 Malic acid
17 penta Sodium triphosphate
18 Potassium dihydrogen orthophosphate
19 Potassium bicarbonate
20 Sodium bicarbonate

21 Sodium carbonate
22 Sodium dihydrogen orthophosphate
23 Sodium hydroxide
24 Sodium malate
25 Sodium sesquicarbonate
26 Sulphuric acid
27 tetra Potassium diphosphate
28 tetra Sodium diphosphate
29 tri Potassium dihydrogen orthophosphate
30 tri Sodium hydrogen orthophosphate

F EMULSIFIERS, STABILISERS, THICKENERS AND GELLING AGENTS

1 Acacia (Gum arabic)
2 Agar
3 Alginic acid
4 Ammonium alginate
5 Ammonium phosphate
6 Calcium alginate
7 Calcium stearoyl-2-lactylate
8 Carboxymethyl cellulose (sodium salt of carboxymethyl ether of cellulose)
9 Carrageenan
10 Collagen
11 Dextrans
12 Disodium ethylenediamine tetracetate (EDTA)
13 Disodium phosphate
14 Ether of poly glycerol and of alcohols obtained by the reduction of oleic and palmitic acids
15 Ethylcellulose
16 Ethylmethylcellulose
17 Furcelleran
18 Gelatin
19 Glycerol
20 Glyceryl polyethylene-glycol ricinoleate
21 Guar gum
22 Hydroxypropyl-methyl cellulose
23 Hydroxypropylcellulose
24 Lecithin
25 Locust bean gum (Carob gum)
26 Mannitol
27 Methylcellulose
28 Micro-crystalline cellulose
29 Mono- and diglycerides of edible fatty acids esterified with the following acids:
(a) acetic
(b) lactic
(c) citric

(d) tartaric
(e) mono- and diacetyl-tartaric

30 Mono- and diglycerides of fatty acids
31 Mono-esters of propylene glycol and edible fatty acids, alone or in mixtures with diesters
32 Monosodium phosphate
33 Partial polyglycerol esters of polycondensed fatty acids of castor oil
34 Pectins
35 Pentasodium triphosphate
36 Polyethylene glycol 6000
37 Polyethylene glycol ester of fatty acids from soya oil
38 Polyglycerol esters of non-polymerized edible fatty acids
39 Polyoxyethylated glyceride of tallow fatty acids
40 Polyoxyethylene (20)-sorbitan monooleate
41 Polyoxyethylene (20)-sorbitan monolaurate
42 Polyoxyethylene (20)-sorbitan monopalmitate
43 Polyoxyethylene (20)-sorbitan monostearate
44 Polyoxyethylene (20)-sorbitan tristearate
45 Polyoxypropylene-polyoxyethylene polymers (Molecular Weight 6800-9000)
46 Potassium alginate
47 Propane-1,2-diol alginate
48 Sodium, potassium and calcium salts of edible fatty acids, alone or in mixtures, derived either from edible fats or from distilled edible fatty acids
49 Propylene glycol
50 Sodium alginate
51 Sodium stearoyl-2-lactylate
52 Sorbitan monolaurate
53 Sorbitan monooleate
54 Sorbitan monopalmitate
55 Sorbitan monostearate
56 Sorbitan tristearate
57 Sorbitol
58 Stearoyl-2-lactylic acid
59 Stearyl tartrate
60 Sucroglycerides (mixture of esters of saccharose and mono- and diglycerides of edible fatty acids)
61 Sucrose esters of fatty acids (esters of saccharose and edible fatty acids)
62 Tamarind seed flour
63 Tragacanth
64 Trisodium phosphate
65 Xanthan gum

F DUST SUPPRESSANTS

1 Castor oil
2 Cod liver oil
3 Mineral oil
4 Paraffin oil

5 Vegetable oils

G DILUENTS AND CARRIERS

1 Alcohol ethoxylate
2 Calcium carbonate
3 Edible grains and their processing by-products
4 Glyceryl diacetate
5 Isopropyl alcohol
6 Isopropylene
7 Mineral oil
8 Oils, fats, carbohydrates, protein extracts and fibre products of edible plant origin, not otherwise specified in this Part
9 Propylene glycol
10 Sodium chloride
11 Vermiculite
12 Whey powder and other milk by-products

H DEODORISERS

1 Extract of Yucca schidigera

I FLAVOURS, FLAVOUR ENHANCERS, SWEETENERS AROMATIC SUBSTANCES AND APPETIZING SUBSTANCES

1 All natural flavour concentrates, natural flavouring substances, nature-identical flavouring substances,natural aromatic raw materials and artificial flavourings
as defined and permitted in Standard A6 of the Food Standards Code
2 Ammonium chloride
3 Butyric acid
4 Calcium saccharin
5 Dextrose
6 Disodium guanylate
7 Disodium inosinate
8 Ethyl butyrate
9 Fructose
10 Glucose
11 Lactose
12 Neohesperidine dihydrochalcone
13 Potassium chloride
14 Saccharin
15 Sodium chloride
16 Sodium saccharin
17 Sucrose
18 Thaumatin

APPENDIX 7 : EXEMPTION LIST AS SINGLE INGREDIENT OF VITAMINS, AMINO ACIDS, MINERALS, ELECTROLYTES & OTHER FOR MANUFACTURING PURPOSE ONLY

VITAMINS

1 Vitamin A
2 Vitamin B1 (Thiamine)
3 Vitamin B2 (Riboflavin)
4 Vitamin B3 (Niacin/Nicotinic Acid/Niaciamide/Nicotinamide)
5 Vitamin B5 (Calcium Pantothenic/Panthenol)
6 Vitamin B6 (Pyridoxine)
7 Vitamin B8 (Inositol)
8 Vitamin B9 (Folic Acid)
9 Vitamin B12 (Cyanocobalamin)
10 Vitamin C (Asocobic Acid/Sodium Ascorbate)
11 Vitamin C Monophosphate
12 Vitamin D3
13 Vitamin E
14 Vitamin H2 (Biotin)
15 Vitamin K3 Menadione Sodium Bisulfite (MSB)
16 Vitamin K3 Menadione Nicotinamide Bisulfite (MNB)
17 Vitamin A/D3
18 Vitamin BT (L-Carnitine)
19 Choline Chloride
20 Beta Carotene

AMINO ACIDS

1 DL-Methionine
2 DL-Methionine Hydroxyl Analog
3 L-Lysine HCL
4 Lysine Sulphate
5 L-Threonine
6 L-Tryptophan*

MINERALS, ELECTROLYTES & OTHERS

1 Cobalt (Carbonate/sulphate/oxide)
2 Copper (Carbonate/ sulphate /oxide)
3 Zinc (Carbonate/ sulphate /oxide)
4 Ferrous (Carbonate/sulphate /oxide)
5 Manganese (Carbonate/ sulphate /oxide)
6 Sodium Selenite
7 Potassium Iodate
8 Potassium Iodide
9 Calcium Iodate
10 Dicalcium Phosphate
11 Mono Dicalcium Phosphate
12 Mono Calcium Phosphate
13 Tricalcium Phosphate
14 Magnesium (Chloride/sulphate/phosphate)

15 Potassium (Chloride/sulphate/phosphate)
16 Sodium (Chloride/sulphate/phosphate)
17 Calcium (Chloride/sulphate/phosphate)
18 Sodium Butyrate
19 Sodium Bicarbonate
20 Sodium Humate
21 Calcium Propionate
22 Calcium Butyrate

*This substance is a Scheduled Poison item as listed in the First Schedule of Poison Act 1952. Therefore, the importation and sale of this substance is still under the jurisdiction of the Poison Act 1952.

APPENDIX 8 : INDICATION AND FUNCTIONAL CLAIMS FOR HEALTH/DIETARY SUPPLEMENT PRODUCT

Dietary/health supplements shall mean 'products that are intended to supplement the diet taken by mouth in the forms such as pills, capsules, tablets, liquids or powders and not represented as conventional food/sole item of a meal or diet'.

Dietary/ Health Supplements may include ingredients such as: vitamins, minerals, amino acids, natural substances of plant/animal origin and substances with nutritional/physiological function.

Allowable Indication or words to that effect:

a) Used as Dietary Supplement

b) Used as Health Supplement

c) Used as Food Supplement

d) Used as Nutritional Supplement

Functional claims are allowed on labels for dietary/health supplements which will generally begin with phrases such as "has a role in …"; "is involved in…"; "Helps in maintenance.."; "helps to…" "required for…", or "needed for…" normal metabolic or physiological functions. The table below contains examples of acceptable functional claims for a product containing the specified vitamin, mineral or amino acid.

ACCEPTABLE FUNCTIONAL CLAIMS

VITAMINS/MINERALS/AMINO ACIDS	***Acceptable 'Functional Claims'***
Vitamin A (Retinol)	• Helps in maintenance of good health • Has a role in maintaining normal vision, skin, bones and muscles • Has a role in maintaining normal growth processes • Is involved in normal reproductive performance • Has a role in maintaining integrity of skin and mucous membranes
Vitamin C (Ascorbic Acid)	• Helps in maintenance of good health • Has a role in maintaining healthy cartilage, tendons and bone
Vitamin D **(D2 – Ergocalciferol)** **(D3 - Cholecalciferol)**	• Helps in maintenance of good health • Has a role in the absorption of calcium & phosphorous • Has a role in normal growth and health of bones and teeth.
Vitamin E (Tocopherol)	• Helps in maintenance of good health • Is an antioxidant
Vitamin B1 (Thiamin)	• Helps in maintenance of good health • Has a role in the metabolism and maintenance of normal muscle and nerve function • Has a role in assisting in the maintenance of normal appetite and bodyweight • Has a role in helping body to metabolize carbohydrates
Vitamin B2 (Riboflavin)	• Helps in maintenance of good health • Is required for normal general metabolism and growth • Has a role in maintaining integrity of skin,

VITAMINS/MINERALS/AMINO ACIDS	*Acceptable 'Functional Claims'*
	mucous membranes • Has a role in helping the body to utilize energy from food/metabolize proteins, fats and carbohydrates
Vitamin B3 (Niacin)	• Has a role in maintaining of good health • Has a role in helping normal growth and development • Has a role in helping the body to utilize energy from food
Vitamin B6 (Pyridoxine)	• Helps in maintenance of good health • Has a role in normal general metabolism, nervous system function and vision • Is involved in red blood cell formation • Has a role in maintaining normal healthy skin and vision • Has a role in helping the body to metabolize proteins, fats and carbohydrates
Vitamin B12 (Cyanocobalamin)	• Has a role in general metabolism, nervous and reproductive function • Has a role in blood cell production
Vitamin K (Menadione)	• Has a role in maintaining normal blood clotting process
Folic Acid	• Involved in general metabolism • Involved in the formation of red and white blood cells and haemoglobin • Has a role in blood cell production
Beta Carotene	• Helps in maintenance of good health • Has a role in maintenance of growth, vision and tissue differentiation

VITAMINS/MINERALS/AMINO ACIDS	*Acceptable 'Functional Claims'*
Biotin	• Helps in maintenance of good health • Helps to metabolize fats and carbohydrates
Choline	• Is involved in metabolism of fats • Has a role in transmitting nerve impulses
Inositol	• Has a role in the metabolism of fats and integrity of hair coat • Has a role in maintaining a normal health coat
Niacin	• Involved in general metabolism and red blood cell formation • Has a role in maintaining normal healthy skin an hair condition
Panthothenic Acid	• Helps in maintenance of good health • Helps to metabolize fats and carbohydrates
Calcium	• Helps in maintenance of good health • Helps in the formation and maintenance of bones and teeth
Chromium	• Has a role in the regulation of glucose metabolism
Cobalt	• Is involved in the formation of vitamin B12 and subsequent formation of red blood cells and hemoglobin • Has a role in maintaining normal nerve cell function
Copper	• Has a role in iron metabolism, bone development, and maintenance of elastic connective tissue
Iodine	• Helps in maintenance of good health • Helps in the function of the thyroid glands

VITAMINS/MINERALS/AMINO ACIDS	*Acceptable 'Functional Claims'*
Iron	• Helps in maintenance of good health • Helps in the formation of red blood cell • Helps to prevent anemia due to iron deficiency
Magnesium	• Helps in maintenance of good health • Helps the body to metabolize carbohydrate
Manganese	• Helps in maintenance of good health • Helps the body to metabolize carbohydrate and proteins
Molybdenum	• Has a role in general metabolism
Potassium	• Has a role in maintaining cellular integrity and healthy nerve and muscle function • Is involved in normal digestion and utilization of dietary nutrients • Has a role in muscular contraction, nerve function and relaxation of the heart muscle
Phosphorus	• Helps in maintenance of good health • Helps in the formation and maintenance of boons and teeth
Selenium	• Has a role in preventing cellular oxidation • Necessary for normal growth and fertility
Sodium and Chloride	• Has a role in maintaining normal electrolyte balance in body tissues during heavy exercise • Has a role in recovery after strenuous exercise
Sulphur	• Has a role in general metabolism and protein synthesis • Has a role in maintaining healthy hair, skin and hooves • Has a role in maintaining normal healthy joints

VITAMINS/MINERALS/AMINO ACIDS	*Acceptable 'Functional Claims'*
Zinc	• Helps in maintenance of good health • Helps to metabolize carbohydrates, fats and protein
Copper	• Helps in maintenance of good health • Helps in the formation of red blood cell
Arginine	• Has a role in promoting release of metabolic hormones-insulin, growth hormone • Is involved in the immune response • Is a component of urea cycle
Histidine	• Is involved in normal growth
Isoleucine	• Is involved in normal protein synthesis and energy production
Leucine	• Has a role in normal protein synthesis and energy production
Lysine	• Has a role in normal protein synthesis
Methionine	• Aids liver in detoxification mechanisms
Phenylalanine	• Has a role in normal protein synthesis
Threonine	• Required for normal growth, feed conversion and nitrogen balance in tissues
Tryptophan	• Has a role in normal growth • Involved in synthesis of niacin (vitamin B3)
Valine	• Has a role in normal energy metabolism and protein synthesis

Reference: Guidelines For Stockfeed Supplement Products Containing Vitamins, Minerals or Amino Acids and Containing Only 'Nutritional Message', Veterinary Guideline No 8, APVMA

APPENDIX 9 : LIST OF PROHIBITED BOTANICALS (HERBS AND HERBAL DERIVATIVES)

(i) Botanicals (and botanical ingredients) containing Scheduled poisons as listed under the Poisons Act 1952

Aconitum

Asidosperma quebracho

Atropa belladona

Black nightshade

Berberis

Calabar bean (physostigma venenosum)

Cabola albarrane (squill)

Chondodendron tomentosum

Colchicum autumnale

Datura metel

Datura stramonium

Digitalis purpurea folium

Drimia maritima (Squill)

Ephedra Herbs

Foxglove leaf

Gelsemium sempervirens

Hyoscyamus muticus

Hyoscyamus niger

Larrea tridenata

Larnea Mekicara

Lobelia inflata

Lobelia nicotianifolia

Mitragyna speciosa Korth. (mitragynine)

Nicotinana Tabacum (solanine)

Nux Vomica

Papaver somniferum

Physostigma veneosum (Calabar Bean)

Pilocarpus microphyllus

Puasinystalia yohimbe

Rauwolfia serpentina

Rauwolfia vomitoria

Schoenocaulonofficinale

Scillae bulbus (Squill)

Solanum nigrum (Black nightshade)

Strychnos nuxvomica

Urginea maritima (Squill)

Urginea Scill (Squill)

Valerian extract (Valepotriates)

(ii) Botanicals (& botanical ingredients) which are banned

1. Dryabalanops aromatica & Borneolum syntheticum (Contain camphor & borneol - not allowed in preparations for oral use)

2. Chapparal (Larrea tridentate & Larrea mexicana)

3. Hydrastis canadensis

4. Magnolia officinalis

5. Stephania tetrandra

6. Piper methysticum (kava-kava)

7. Aristolochic Acid**

8. Comfrey (Symphytum officinale, S. asperum, S. x. uplandicum)

9. Senacio spp (Senecio aureus, S.jacobaea, S. bicolor, S. nemorensisi, S vulgaris, S. longilobus, S. scandens Buch.-Ham)

**** For list of the Botanicals which may contain Aristolochic Acid (A. A.), please refer to Drug Registration Guidance Document (Human Products):**

a) List A - Botanicals Known or Suspected to contain Aristolochic Acid;
b) List B - Botanicals which may be Adulterated with Aristolochic Acid

APPENDIX 10 : LIST OF INGREDIENTS (ACTIVE) NOT ALLOWED TO BE REGISTERED BY THE DRUG CONTROL AUTHORITY

This is not an exhaustive list, it will be reviewed when necessary.

A. Ingredients not allowed in veterinary products

1. Avoparcin

B. Ingredients not allowed for food-producing animals and aquacultures

1. Chloramphenicol

2. Nitrofurans such as :
   - i) Nitrofurantoin
   - ii) Nitrofurazone
   - iii) Furazolidone
   - iv) Furaltadone

3. Beta agonists such as :
   - i) Salbutamol
   - ii) Terbutaline
   - iii) Clenbuterol
   - iv) Fenoterol
   - v) Salmeterol
   - vi) Bambuterol HCl
   - vii) Bitolterol Mesilate
   - viii) Broxaterol
   - ix) Eformoterol fumarate
   - x) Pirbuterol HCl
   - xi) Procaterol HCl
   - xii) Reproterol HCl
   - xiii) Rimiterol HBr
   - xiv) Tretoquinol HCl
   - xv) Tulobuterol HCl

4. Chlorpromazine

5. Carbadox

6. Olaquindox

7. Chloroform

8. Colchicine

9. Dapsone

10. Nitroimidazole such as :
    - i) Dimetridazole
    - ii) Ipronidazole
    - iii) Metronidazole

iv) Ronidazole

11. Teicoplanin
12. Vancomycin

B. Any products containing Chlorofluorocarbon

C. Combinations not allowed in veterinary products

1. Combinations of Herbal with other drugs:
1.1 Herbal + Scheduled poison
1.2 Herbal + OTC

APPENDIX 11 : GUIDELINE FOR STABILITY DATA

The purpose of stability testing is to provide evidence on how the quality of a product, in its proposed marketing packaging, varies with time under the influence of a variety of environmental factors, such as temperature, humidity and light, and enables recommended storage conditions and shelf lives to be established.

1. Size and number of batches tested

The overall quality of the product batches of the formulation used in stability testing should be representative of the quality of the formulation to be made on a production scale.

Stability data from 2 current batches (preferably pilot and/or production scale) is considered by the DCA to be the statistical minimum necessary to establish a shelf life for a product.

Therefore when data from less than the minimum two batches are provided the applicant should include a valid scientific argument justifying the suitability of the data provided for establishing the proposed shelf life.

The batch identity, date of manufacture and batch size should be reported with the stability data.

2. Containers

The product should be packaged in the same containers (materials and size) that are proposed for the marketing of the final product.

If the product will be marketed in containers of differing materials, then all proposed containers should be trialled.

If the product is to be marketed in containers in which stability testing would be impractical (e.g., too large), then stability trials in smaller containers of the same materials and construction may be used to extrapolate to the larger containers.

3. Bracketing

Bracketing design may be used if the product strengths are very closely related in composition, such as,

1. a tablet range made with different compression weights of a similar basic granulation, or
2. a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells, or
3. bottles containing 100 tablets and bottles containing 1000 tablets, or
4. bottles containing 100 mL of a product and bottles containing 500 mL of the product.

Bracketing can be applied to different container sizes or different fills in the same container closure system. For example, where the same strength and exact container/closure system is used for three or more fill contents, the manufacturer may elect to place only the smallest and largest container closure system into the stability program.

An example of bracketing design is given in the table below:

Table 1-1 Bracketing design

Strength		**50 mg**			**75 mg**			**100 mg**		
Batch		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
Container size	**100 mL**	√	√	√				√	√	√
	250 mL									
	500 mL	√	√	√				√	√	√

4. Storage condition

Storage stability programmes should include real time studies or a combination of real time and accelerated conditions. Recommended storage conditions from the labeling of Veterinary Products are listed below:

Store below –18℃ (deep freeze);

Store below –5℃ (freeze);

Store between 2℃ and 8℃ (refrigerate. Do not freeze);

Store below 8℃ (refrigerate);

Store below 25℃ (air conditioning);

Store below 30℃ (room temperature).

The temperature at which samples are stored at (e.g., real time and/or accelerated conditions) will impact on how the stability data are interpreted and the length of shelf life that can be recommended. Recommended storage conditions are as follows:

Table 1-2 Recommended storage conditions (temperatures and relative humidities)

Proposed storage temperature (product label)	Real time testing (Minimum 2 batches)	Accelerated testing (Minimum 2 batches)
Products intended for Storage in a freezer	-20℃±5℃	Accelerated trial probably not appropriate
Products intended for Storage in a refrigerator	5℃ ±3℃	25℃ ±2℃ and 60% RH ±5% RH
25℃ (air conditioning)	25℃ ±2℃ and 60% RH ±5% RH	35 - 40℃ ±2℃ and 75% RH ±5% RH
30℃ (room temperature)	30℃ ±2℃ and 75% RH ±5% RH	40 - 45℃ ±2℃ and 75% RH ±5% RH

5. Testing intervals

Samples should be tested as soon as practicable following manufacture, and then every 3 months over the first year, every 6 months over the second year and at 12-month intervals thereafter. The dates of product testing should be recorded and reported with the stability data.

6. Test parameters

The stability study should cover those features susceptible to change during storage and likely to influence the quality, safety and efficacy of the product. Test parameters to be measured in a stability trial are determined by the dosage form/formulation type and may include:

- Physical properties of the product;
- Organoleptic properties (taste, odour, etc.);
- Active ingredient content and formation of toxic degradation products;
- The content of other important components of the formulation (e.g., antimicrobial preservatives);
- Microbial properties (where appropriate); and

Relevant test parameters for each type of dosage form are given in Attachment C. It is expected that all relevant parameters will be addressed in a stability trial. If certain parameters are not addressed relevant scientific argument should be provided as to why testing was not required.

7. Expiry specification

An expiry specification is the combination of physical, chemical, biological and microbiological test requirements that a veterinary chemical product must meet throughout its shelf life. The range of values that each test parameter must fall within throughout the shelf life of the product should be provided. These are often referred to as “check specifications” or “expiry specifications”.

8. Duration of stability trials

(i) Locally manufactured product

At point of submission, 3 months accelerated data (45-50℃/75% RH ±5% RH) or 6 months accelerated data (40℃/75% RH ±5% RH) and a commitment letter to submit real time stability data once available is required to claim for 3 years shelf life.

(ii) Imported product

A minimum of 12 months real time stability data with a complete accelerated data are required during submission to claim for 2 years shelf life

(iii) Minerals

For products (excluding parenteral products) containing minerals as the only active substance, a shelf life of 18 months for liquid products and 24 months for solid products may be approved without evaluation of any supporting stability data in the submission, provided the label advice indicates the product should be stored at room temperature (below 30℃).

(iv) Vitamins and Minerals

In the case of products (excluding parenteral products) which contain vitamins, or vitamins and minerals as the only active substance a shelf life of 12 months may be approved without evaluation of any supporting stability data in the submission, provided the label advice indicates the product should be stored under air conditioning (below 25℃) and protected from light, and provided there is no information available suggesting interactions occur between substances which are likely to shorten the stability of the vitamin(s), e.g., iron and vitamin E interaction.
In any case where an applicant proposes a different shelf life, stability data and/or argument should be provided to support this.

9. Testing requirements for specific veterinary chemical product types

(i) Controlled-release dosage forms

In addition to the specific stability tests that are required for the particular dosage form, the stability study should include the dissolution test to determine the rate of release of the active substance.

(ii) Intramammary products

Intramammary products are solutions, emulsions, suspensions or semi-solid preparations containing one or more active substances in a suitable vehicle. In addition to the parameters relevant to particular dosage forms, a test for sterility must be performed.

(iii) Oral drenches

Drenches for oral administration are available as powders or concentrated solutions or suspensions. They are also available as solutions or suspensions ready for use. Parameters relevant to particular dosage forms should be monitored in the stability study.

(iv) Veterinary liquid products for cutaneous applications

Veterinary liquid products for cutaneous applications are liquid preparations intended to be applied to the skin to obtain a local and/or a systemic effect. Veterinary liquid products for cutaneous applications include dip concentrates, pour-on, spot-on, sprays, teat dips, teat sprays and udder-washers. These preparations may be supplied as concentrates or ready-to-use products. They are solutions, emulsions or suspensions containing one or more active substance in a suitable vehicle. In addition to the parameters relevant to particular dosage forms, stability data on diluted dipping/jetting and teat sprays products are required.

10. Additional Tests

i) Parenteral products

(a) Stability of reconstituted products

The in-use stability of parenteral veterinary products that are reconstituted prior to administration, or diluted prior to use, or claimed to be stable when mixed with other products, or where the product may be labile once the container is opened, must be demonstrated,

Note: the in-use stability data for reconstituted products and for parenteral products supplied in multi-dose containers is not required if the product label contains a disposal statement to the effect “To avoid microbial contamination, unused portions of the product must be discarded within 24 hours after reconstitution or first broaching of the container”.

(b) In-use stability testing

The in-use stability test should be designed to simulate the use of the product in practice. The product should be stored as recommended on the product label throughout the duration of the test. A storage condition recommendation for the product after first use may be specified on the label that is different to the unopened container storage conditions.

ii) Sterile eye and ear preparations in multiple dose containers

For sterile eye and ear preparations packaged in multi-dose containers, in-use (broached container) testing is required if the product is not used within four weeks after opening the container.

Note: the in-use testing is not required if the product label states that the product be used within 4 weeks of opening the container.

iii) Sterility requirements for product stated to be sterile

Sterility should be considered as part of the shelf life of a veterinary chemical product stated to be sterile. The samples should be tested on the initial date and at the proposed expiration date.

- **Injectables**

Sterility testing should be demonstrated for all injectable veterinary chemical products (including intra-mammary products) except euthanasia products and ear implants for bovine and ovine species.

- **Ophthalmic products**

Sterility should be demonstrated for all ophthalmic products.

- **Ampoules**

Sterility should be demonstrated on sealed ampoules only on the date of manufacture. Since the ampoules are hermetically sealed, this type of seal prevents microbial contamination.

- **Sterile products with microbial inhibitors**

Veterinary chemical products containing preservatives (microbial inhibitors) to control microbial contamination should be tested for preservative contents at reasonable intervals in the stability trial. This may be accomplished by microbial challenge test (e.g., Efficacy of Antimicrobial Preservation of the BP or Antimicrobial Preservative Effectiveness Test of the USP) and by performing chemical assays for the preservatives during the regular stability testing schedules. If a lack of or low levels are found, testing for sterility should be carried out.

iv) Dissolution testing

The dissolution test for solid dosage forms is a physical quality control test designed to ensure the consistency of active substance release from the dosage form and assure consistent batch-to-batch behaviour. Dissolution data should be generated on at least 6 individual units at each test station.

11. Interpretation of stability data and recommendation of product shelf life

This section clearly defines the maximum shelf life that can be recommended on the basis of a given stability data set. The information will be of benefit to applicants developing stability testing programs for veterinary chemical products and it will give added transparency and consistency to the assignment of product shelf lives.
Real time studies, or a combination of real time and accelerated studies, should be provided to support the proposed shelf life.

i) Real time stability data

The real time stability data should be generated by storing the product under the proposed (label) storage conditions for the product. The maximum shelf life that will be recommended based on evaluation of real time data is as follows: Where product samples exhibit adequate stability when stored for Y months at temperature X℃,

then a shelf life of Y months may be recommended where the normal (label) storage conditions of the product specify storage at or below X℃.

ii) Accelerated stability data

Accelerated stability testing studies are designed to increase the rate of chemical degradation or physical change of a veterinary chemical product by using exaggerated storage conditions. In general, accelerated stability trials should be conducted at a storage temperature 10 – 15℃ above the proposed storage temperature. The accelerated data should be supported by real time data of the same stability trial duration. Where no significant change occurs at the accelerated condition, the maximum shelf life that will be recommended based on evaluation of real time plus accelerated data is as follows:

Table 1-4 Shelf life based on accelerated stability data

Stability data type	Duration of stability trial	Maximum shelf life
Real time + accelerated	Up to 12 months	Twice the duration of the trial
Real time + accelerated	X* months	X + 12 months

X* = GREATER THAN 12 MONTHS

Example 1: The proposed storage condition for a product is 'store below 30℃ (room temperature)'. Stability data for 3 batches stored for 12 months at 30℃ and 40 - 45℃ are provided in the application. The maximum shelf life that the NPCB will recommend for the product on the basis of the submitted data is 24 months when stored below 30℃ (room temperature).

Example 2: The proposed storage condition for a product is store 'below 30℃ (room temperature)'. Stability data for 3 batches stored for 18 months at 30℃ and 40 - 45℃ are provided in the application. The maximum shelf life that the NPCB will recommend for the product on the basis of the submitted data is 30 months (i.e., 18 + 12 months) when stored below 30℃ (room temperature).

ATTACHMENT C

PARAMETERS/CHARACTERISTICS OF THE PRODUCT TO BE TESTED IN STABILITY TRIALS

Veterinary products that are the subject of an individual monograph in a recognized pharmacopoeia [BP, BP (Vet), Ph Eur and USP] are required to comply with the requirements stated in the monograph. The following list of parameters for each dosage form is presented as a guide for the type of tests to be included in a stability study. In general, appearance and assay tests should be performed for all dosage forms.

The list of test parameters presented for each dosage form is not intended to be exhaustive, nor it is expected that every listed test be included in the design of a

stability protocol for a particular veterinary chemical product (for example, a test for odour should be performed only when necessary and with consideration for safety of the analyst).

Dosage form	Recommended Test Parameters
Aerosols (pressurised pharmaceutical preparations)	Identification of the Active substance Active substance assay Preservative content (where appropriate) Delivered dose or dose per actuation Particle size distribution (suspensions only) Number of metered doses
Capsules	Appearance Identification of the active substance Uniformity of content/mass Active substance assay Impurities (where appropriate) Disintegration time Dissolution profile (where appropriate)
Collars/ear tags	Appearance Identification of the active substance Uniformity of content/mass Active substance assay Dissolution profile (release of active substance from the inert matrix)
Emulsions	Appearance (including phase separation) Identification of the active substance Active substance assay Preservative content (where appropriate) pH Viscosity Microbial Limits
Granules	Appearance Identification of the active substance Active substance assay Moisture content Uniformity of content/mass (for single dose preparations only) Dissolution profile (where appropriate)
Implants (sub-cutaneous, intravaginal)	Appearance Identification of the active substance Active substance assay Uniformity of content/mass Hardness Friability Moisture content (where appropriate) Dissolution profile (release of the active substance from the inert matrix)

Dosage form	Recommended Test Parameters
Injectables	Appearance, colour, clarity Identification of the active substance Particulate matter Active substance assay Impurities (where appropriate) Preservative content (where appropriate) Sterility (where appropriate) Bacterial endotoxins -Pyrogens pH (aqueous preparations only)
Oral powders	Appearance Identification of the active substance Active substance assay Moisture content (where appropriate) Microbial Limit
Paste	Appearance Identification of the active substance Active substance assay Viscosity Microbial Limit
Powders for injection	Appearance Identification of the active substance Active substance assay Impurities (where appropriate) pH of reconstituted solution Sterility testing for reconstituted solutions (where appropriate) **Note: In-use shelf life of reconstituted product should not exceed 24 hours unless justified by providing stability data to show that the reconstituted product is stable for the length of time stated on the label.**
Soluble powders in drinking water	Appearance Identification of the active substance Active substance assay pH of solution **Note: In-use shelf life of medicated drinking water should not exceed 24 hours unless justified by providing stability data to show that the active substance is stable for the length of time stated on the label**
Solutions	Appearance (e.g. cloudiness, precipitation, clarity of solution) Identification of the active substance pH (aqueous solutions only) Active substance assay Impurity content (where appropriate) Preservative content (where appropriate) Sterility (where appropriate) Viscosity (where appropriate) Specific gravity (where appropriate) Microbial Limit

Dosage form	Recommended Test Parameters
Suppositories	Appearance Identification of the active substance Active substance assay Microbial Limit Dissolution
Suspensions	Appearance Identification of the active substance pH (aqueous suspensions only) Viscosity (where appropriate) Active substance assay Particle size distribution (where appropriate) Preservative content (where appropriate) Microbial Limit
Tablets	Appearance Identification of the active substance Active substance assay Impurities (where appropriate) Tablet hardness Friability (uncoated tablets) Disintegration time Dissolution profile (where appropriate) Uniformity of content/mass Uniformity of weight **Note: For chewable tablets, testing for disintegration time and dissolution profile is not required.**
Topical, ophthalmic and otic products (e.g., powders, ointments, creams, lotions, gels and pastes)	Appearance, colour, clarity and odour Identification of the active substance Active substance assay Preservative content (where appropriate) pH Microbial limits/sterility (where appropriate) **Note: For ophthalmic products (creams, solutions, suspension and ointments), testing for sterility is required.**

Reference: Guidelines For The Generation of Storage Stability Data of Veterinary Chemical Products, Veterinary Guideline No 68, APVMA

APPENDIX 12 : ALLOWABLE MAXIMUM RESIDUAL LIMIT (MRL)

This is not an exhaustive list. MRL not in the list but available in MRL list of Codex alimentarius, EMEA,Canada, USFDA, Japan NDA & Australia is allowed. Product containing ingredient not listed in MRL list from the countries mentioned will not be considered to be registered.

A) MAXIMUM PERMITTED PROPORTION OF DRUG RESIDUES IN FOOD

The food specified in column (2) of the Table below shall not contain the drug specified in column (1) thereof in proportions greater than the maximum permitted proportions specified opposite and in relation to that food in column (3) thereof.

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
Albendazole	2-Aminosulfone metabolite	Muscle, fat (cattle and other species), milk (cattle)	100
		Liver, kidney (cattle and other species)	5000
Amoxicillin	Amoxicillin	Milk (cattle)	4
		Muscle, liver, kidney, fat (all food producing species)	50
Ampicillin	Ampicillin	Milk (cattle)	4
		Muscle, liver, kidney, fat (all food producing species)	50
Amprolium	1-4 amino-2-n-propyl-5-(pyrimidinylmethyl)-2-picolinium chloride hydrochloride	Muscle (chicken, turkey, pheasant and calf), liver (calf), kidney (calf)	500
		Liver (chicken, turkey and pheasant), kidney (chicken and turkey)	1000
		Fat (calf)	2000
		Egg (chicken and turkey)	4000
Azaperone	Sum of azaperone and azaperol	Muscle, fat (pig)	60
		Liver, kidney (pig)	100
Benzylpenicillin	Benzylpenicillin	Milk (cattle)	4
		Liver, kidney, muscle (cattle and pig)	50
Carazolol	Carazolol	Muscle, fat (pig)	5
		Liver, kidney (pig)	25
Carprofen	Carprofen	Muscle (horse)	50
		Fat (horse)	100

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
		Muscle, fat (cattle)	500
		Liver, kidney (cattle and horse)	1000
Cefquinome	Cefquinome	Milk (cattle)	20
		Muscle, fat (cattle)	50
		Liver (cattle)	100
		Kidney (cattle)	200
Ceftiofur sodium	Desfuroylceftiofur	Milk (cattle)	100
		Muscle (pig and cattle)	200
		Fat (pig and cattle)	600
		Liver (pig and cattle)	2000
		Kidney (pig and cattle)	4000
Clorsulon	Clorsulon	Muscle (cattle)	100
		Liver (cattle)	200
		Kidney (cattle)	300
		Fat (cattle)	400
Closantel	Closantel	Muscle, liver (cattle)	1000
		Muscle, liver (sheep)	1500
		Fat (sheep)	2000
		Kidney, fat (cattle)	3000
		Kidney (sheep)	5000
Cloxacillin	Cloxacillin	Milk (cattle)	30
		Muscle, liver, kidney, fat (all food producing species)	300
Colistin	Colistin	Milk (cattle)	50
		Muscle, liver, fat (cattle, chicken, pig, rabbit and sheep)	150
		Kidney (cattle, chicken, pig, rabbit and sheep)	200
		Egg (chicken)	300
Danofloxacin	Danofloxacin	Fat (cattle)	200
		Muscle (cattle and chicken)	300
		Kidney (cattle)	500
		Fat (chicken)	600
		Liver (cattle)	900
		Liver, kidney (chicken)	1200
Decoquinate	Decoquinate	Muscle, liver, kidney, fat (cattle and sheep)	500
Dexamethazone	Dexamethazone	Milk (cattle)	0.3
		Muscle, kidney (cattle, horse and pig)	0.5

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
		Liver (cattle and pig)	2.5
Dicloxacillin	Dicloxacillin	Milk (cattle)	30
		Muscle, liver, kidney, fat (all food producing species)	300
Dihydrostreptomycin	Dihydrostreptomycin	Milk (cattle)	200
		Muscle, liver, fat (cattle, chicken, pig and sheep)	500
		Kidney (cattle, chicken, pig and sheep)	1000
Diminazene	Diminazene	Milk (cattle)	150
		Muscle (‘cattle)	500
		Kidney (cattle)	6000
		Liver (cattle)	12000
Doramectin	Doramectin	Muscle (cattle)	10
		Kidney (cattle)	30
		Liver (cattle)	100
		Fat (cattle)	150
Doxycycline	Doxycycline	Muscle (cattle, pig and poultry)	100
		Liver (cattle, pig and poultry), fat (pig and poultry)	300
		Kidney (cattle, pig and poultry)	600
Enrofloxacin	Sum of enrofloxacin and ciprofloxacin	Muscle, liver, kidney (cattle, chicken and pig)	30
Erythromycin	Erythromycin	Milk (mammalian)	40
		Edible offal, muscle, egg (mammalian and poultry)	300
Estradiol-l7β	Estradiol-17β	Food of bovine origin	GAHP*
Ethopabate	Ethopabate	Muscle (chicken)	500
		Liver, kidney (chicken)	1500
Febantel	Sum of febandazole, oxfendazole and oxfendazole sulfone	Milk (cattle) muscle, kidney, fat (cattle, pig and sheep)	100
		Liver (cattle, pig and sheep)	500
Fenbendazole	Sum of febandazole, oxfendazole and	Milk (cattle), muscle, kidney, fat (cattle, pig and	100

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
	oxfendazole sulfone	sheep) Liver (cattle, pig and sheep)	500
Florfenicol	Sum of florfenicol and its metabolites measured as florfenicol-amine	Muscle (cattle)	200
		Kidney (cattle)	300
		Liver (cattle)	3000
Flubendazole	Flubendazole	Muscle, liver (pig)	10
		Fat (pig)	20
		Fat (cattle)	40
		Liver (cattle)	100
		Muscle (poultry)	200
		Egg (poultry)	400
		Liver (poultry)	500
Flumequine	Flumequine	Muscle, fat (cattle, pig, poultry and sheep)	50
		Liver (cattle, pig, poultry and sheep)	100
		Kidney (cattle, pig, poultry and sheep)	300
Flumethrin	Flumethrin	Edible offal, muscle and milk (cattle)	50
Gentamicin	Gentamicin	Milk (cattle), muscle, fat (cattle and pig)	100
		Liver (cattle and pig)	200
		Kidney (cattle and pig)	1000
Isometamidium	Isometamidium	Muscle, fat, milk (cattle)	100
		Liver (cattle)	500
		Kidney (cattle)	1000
Ivermectin	22, 23 Dihydroavermectin B1a	Liver (pig and sheep)	15
		Fat (pig and sheep)	20
		Fat (cattle)	40
		Liver (cattle)	100
Levamisole	Levamisole	Muscle, kidney ,fat (cattle, pig, poultry and sheep)	10
		Liver (poultry)	100
Lincomycin	Lincomycin	Edible tissue (pig)	100
Maduramicin	Maduramicin	Edible tissue, muscle, (chicken)	240
		Fat (chicken)	480
		Liver (chicken)	720
Moxidectin	Moxidectin	Muscle (deer), liver (cattle)	20

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
		Liver (sheep), kidney (deer), fat (cattle and sheep)	50
		Liver (deer), kidney (cattle and sheep)	100
		Fat (deer), milk (cattle and sheep)	500
Neomycin	Neomycin	Muscle, liver, fat (chicken, turkey, duck, cattle, goat, sheep and pig), egg (chicken), milk (cattle)	500
		Kidney (chicken, turkey, duck, cattle, goat, sheep and pig)	1000
Nicarbazin	Nicarbazin	Muscle, liver, kidney (chicken)	4000
Nystatin	Nystatin	Edible tissue (pig and	0
		poultry), egg (poultry)	
Oxacillin	Oxacillin	Milk (all food producing species)	30
		Muscle, liver, kidney, fat (all food producing Species)	300
Oxfendazole	Sum of fenbendazole, oxfendazole and oxfendazole sulfone	Muscle, kidney, fat (cattle, pig and sheep), milk (cattle)	100
		Liver (cattle, pig and sheep)	500
Oxibendazole	Oxibendazole	Milk (cattle and sheep)	50
		Muscle, liver, kidney, fat (cattle, horse, pig and sheep)	100
Oxytetracycline	Oxytetracyline	Fat (cattle, sheep, pig, chicken and turkey)	10
		Milk (cattle), muscle (cattle, sheep, pig, chicken and turkey)	100
		Egg (chicken)	200

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
		Liver (cattle, sheep, pig, chicken and turkey)	300
		Kidney (cattle, sheep, pig, chicken and turkey)	600
Penicillin	Penicillin	Edible tissue (chicken, quail, pig and sheep), egg (chicken and quail), milk (cattle)	0
		Edible tissue (turkey)	10
		Edible tissue (cattle)	50
Phoxim	Phoxim	Edible offal, muscle (pig)	10
		Fat (pig)	50
Progesterone	Progesterone	Food of bovine origin	GAHP*
Ractopamine	Ractopamine	Muscle (pig)	10
		Fat (pig)	10
		Liver (pig)	40
		Kidney (pig)	90
Robenidine hydrochloride	Robenidine Hydrochloride	Edible tissue (poultry)	100
		Fat (poultry)	200
Salinomycin	Salinomycin	Egg (poultry)	20
		Muscle (cattle)	50
		Edible offal (pig), muscle (pig and poultry)	100
		Edible offal (cattle and poultry)	500
Sarafloxacin	Sarafloxacin	Fat (chicken)	10
		Liver (chicken)	100
Spectinomycin	Spectinomycin	Milk (cattle)	200
		Muscle (cattle, chicken and pig)	300
		Fat (cattle, chicken and pig)	500
		Liver (cattle, chicken and pig)	2000
		Kidney (cattle, chicken and pig)	5000
Spiramycin	Expressed as spiramycin equivalents antimicrobially active residues Sum of spiramycin and neospiramycin	Muscle (pig)	200
		Kidney, fat (pig)	300
		Liver (pig)	600
		Muscle (cattle and chicken), milk (cattle)	200
		Kidney (cattle), fat (cattle and chicken)	300

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
		Liver (cattle and chicken)	600
		Kidney (chicken)	800
Streptomycin	Streptomycin	Milk (cattle)	200
		Muscle, liver, fat (cattle, chicken, pig and sheep)	500
		Kidney (cattle, chicken, pig and sheep)	1000
Sulphadiazine	Sulphadiazine	Edible offal (mammalian), muscle (mammalian), milk (cattle)	100
Sulphadimethoxine	Suiphadimethoxine	Milk (cattle)	10
		Edible offal, muscle	100
		(cattle and chicken)	
Sulphadimidine	Sulphadimidine	Milk (cattle)	25
		Edible offal (chicken and mammalian), muscle (chicken and mammalian), liver, kidney, fat (cattle)	100
Suiphamethazine	Sulphamethazine	Edible tissue (cattle, turkey, chicken and pig)	100
Sulphaquinoxaline	Sulphaquinoxaline	Edible offal, muscle (poultry)	100
Sulphonamide	Sulphonamide	Muscle, liver, kidney, fat (all food producing species), milk (cattle)	100
Testoterone	Testoterone	Food of bovine origin	GAHP*
Tetracycline	Sum of parent drug and its 4-epimer	Muscle (cattle, poultry, pig and sheep), milk (cattle)	100
		Egg (poultry)	200
		Liver (cattle, poultry, pig and sheep)	300
		Kidney (cattle, poultry, pig and sheep)	600
Thiabendazole	Sum of thiabendazole and 5-hydroxy-thiabendazole	Muscle, liver, kidney and fat (cattle, pig, goat and sheep), milk (cattle and goat)	100
Tiamulin	8-alpha-hydroxymutilin	Muscle (pig)	3600
		Liver (pig)	10800
		Kidney, fat (pig)	14400
Tilmicosin	Tilmicosin	Milk (sheep)	50

Substance	Drug Definition of residues in which MRL was set	Food	Maximum Residue Limits (MRLs) in food µg/kg
		Mucle, fat (cattle, poultry, pig and sheep)	100
		Kidney (cattle and sheep)	300
		Liver (cattle and sheep),	1000
		kidney (pig)	
		Liver (pig)	1500
Trenbolone acetate	β-Trenbolone ά-Trenbolone	Muscle (cattle)	2
		Liver (cattle)	10
Triclabendazole	5-chloro-6-(2',3'-dichloro-phenoxy) benzimidazole-2-one	Fat (cattle and sheep)	100
Trimethoprim	Trimethoprim	Edible offal, muscle (mammalian and chicken), egg (chicken), milk (cattle)	50
Tylosin	Tylosin	Milk (cattle)	50
		Muscle, liver, kidney (chicken and cattle), edible tissue (cattle), fat (chicken), egg (chicken)	200
Virginiamycin	Virginiamycin	Muscle, liver, kidney, fat (cattle)	0
		Muscle (pig and poultry)	100
		Fat (poultry)	200
		Liver (pig and poultry)	300
		Kidney, fat (pig)	400
		Kidney (poultry)	500
Zeranol	Zeranol	Muscle (cattle)	2
		Liver (cattle)	10

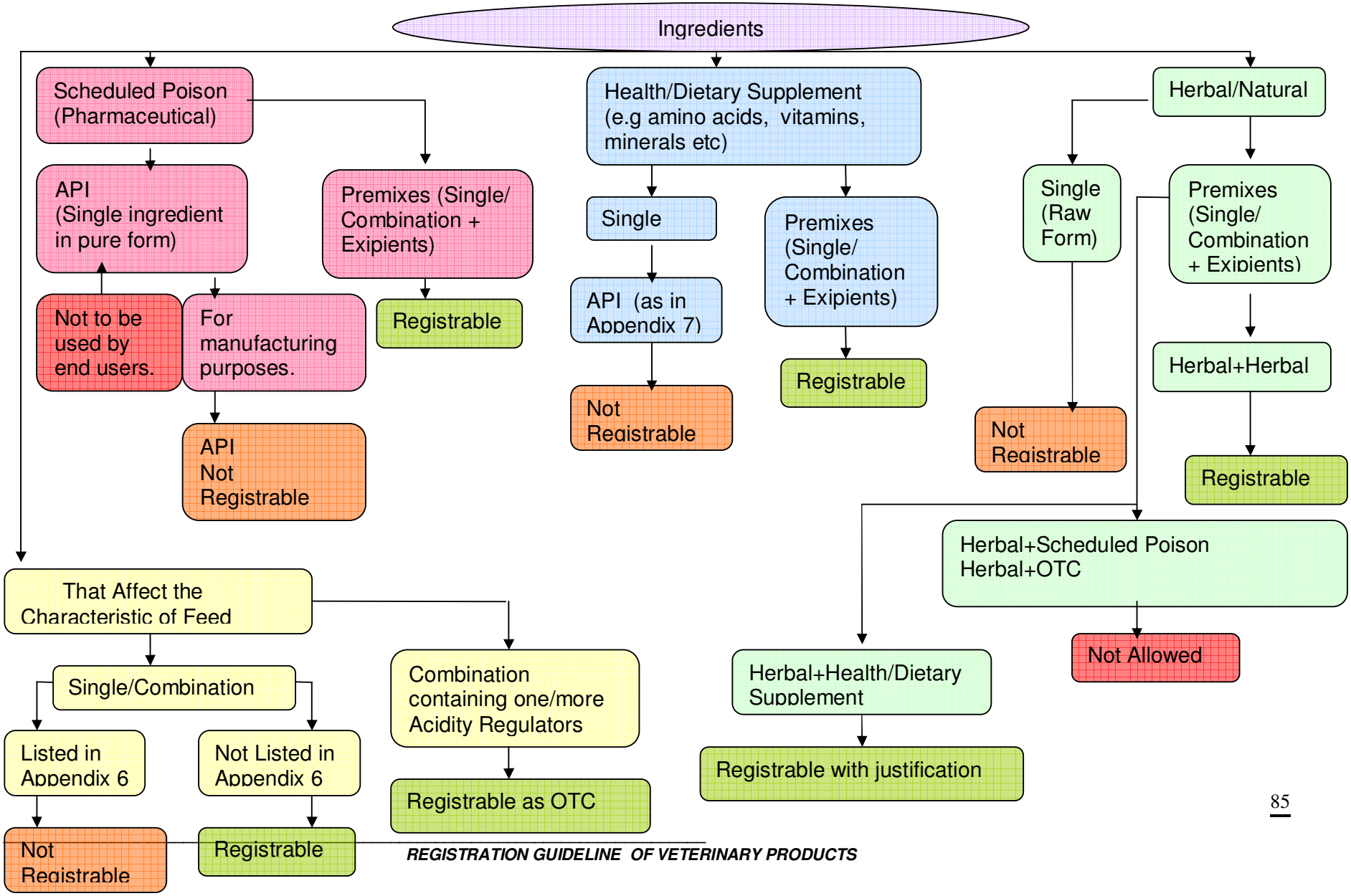
** Good animal husbandry practice*

Reference: Adopted list from Fifteenth A Schedule, [Regulation 40], Food Act 1985

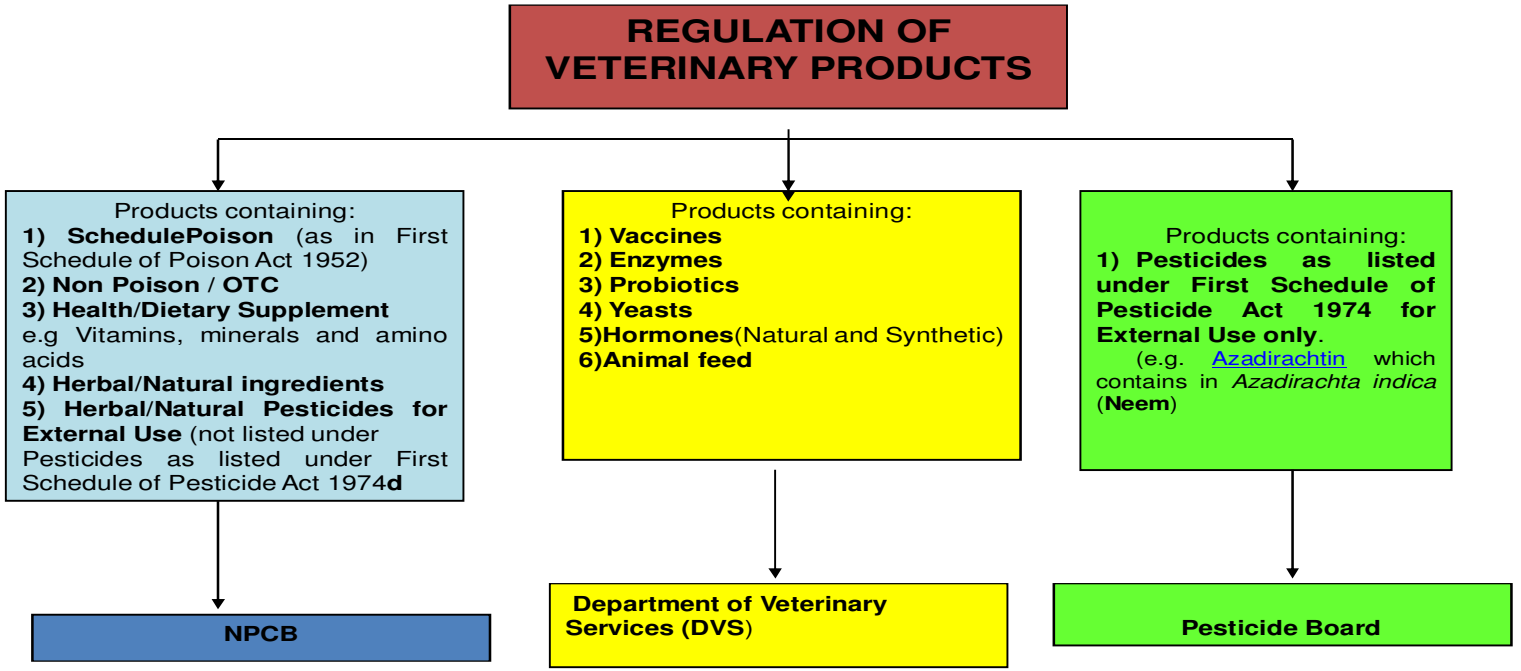
B) MAXIMUM PERMITTED PROPORTION OF DRUG RESIDUES IN AQUACULTURE AND ALLOWABLE WITHDRAWAL PERIOD

BIL	PHARMACOLOGICALLY ACTIVE SUBSTANCES				MRLs µg/kg (ppb)	WITH DRAWAL PERIOD
1	Anti-infectious agents	Antibioticss	Sulfonamides	Sulfonamide	100	30 days
2			Diamino pyrimidine derivatives	Trimethoprim	50	30 days
3			Penicilin	Amoxicyllin	50	30 days
4				Ampicillin	50	30 days
5				Benzylpenicillin	50	30 days
6				Cloxacillin	300	30 days
7				Dicloxacillin	300	30 days
8				Oxacillin	300	30 days
9			Quinolones	Danofloxacin	100	30 days
10				Difloxacin	300	30 days
11				Enrofloxacin	100	30 days
12				Flumequine	600	30 days
13				Oxolonic acid	100	30 days
14			Macrolides	Erythomicyin A	200	30 days
15				Tilmicosin	50	30 days
16				Tylosin	100	30 days
17			Florfenicol	Florfenicol	1000	30 days
18			Tetracyclines	Chlortetracycline	100	30 days
19				Oxytetracycline	100	30 days
20				Tetracycline	100	30 days
21			Lincosamides	Lincomycin	100	30 days
22				Neomycin	500	30 days
23				Paromomycin	500	30 days
24				Spectinomycin	300	30 days
25			Polymyxins	Colistin	150	30 days
26	Antiparasitic Agents	Agents acting against ectoparasites	Organophosphates	Deltamethrin	10	30 days
27		Agents acting against endo- and ectoparasites	Avermectins	Emamectin	100	30 days
28		Dyes		Malachite green	2	30 days

APPENDIX 13 : CLASSIFICATION OF INGREDIENTS FOR VETERINARY USE



APPENDIX 14 : REGULATION OF VETERINARY PRODUCTS IN MALAYSIA



2

SECTION 2
GUIDE ON HOW TO FILL THE ONLINE APPLICATION FORM FOR A PRODUCT REGISTRATION

GUIDE ON HOW TO FILL THE ONLINE APPLICATION FORM

FOR A PRODUCT REGISTRATION

1. Separate modules are available for pharmaceuticals for human use and veterinary use. Please ensure that you click on the appropriate section of the display panel and fill the correct application form.

   {NOTE: THE PROCESSING FEE, ONCE PAYMENT HAS BEEN CONFIRMED, CANNOT BE REFUNDED}

2. The following guidance notes are arranged according to the layout of the application form. USER GUIDE is used whilst this guide, applicants are advised to download the USER GUIDE from NPCB website. www.bpfk.gov.my

3. Attachments can only be made where there is a specific sign.

4. Applicants who are attempting to fill up this form for the first time are advised to familiarise themselves with the drug registration system in Malaysia by reading Section 1 of this guidance document.

5. The technical requirements for pharmaceuticals have already been addressed elsewhere, (such as in the VICH & ASEAN guidelines), and applicants are advised to refer to these guidelines.

Any application for a product registration follows a 2-step process:

STEP 1: PRODUCT VALIDATION FORM

- All fields are compulsory.
- Option is given to accept the validation result and submit, or override and manually select.
- Once validation is verified and submitted, the appropriate application form (Step 2) will be displayed.
- Information entered in Step I will be captured in the data base and need not be re-entered at Step 2.

[1] PRODUCT NAME

To enter product name, dosage form and strength

(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".]**

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.

This name will be shown on the product labeling i.e. inner label, outer carton, package insert and product 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.

[2] DOSAGE FORM

Please select from given list. A tablet may be plain, chewable, coated (enteric, film, or sugar), dispersible, effervescent, extended release, sublingual, etc. The form that correctly describes it in terms of its product quality control specifications and performance should be selected.
A separate application for registration is required for each dosage form.

[3] ACTIVE SUBSTANCE

Substance Name: Please pick substance name from the search database. If substance is not listed, please click the Not Listed Substance button and fill in

the required information.. Please ensure that the spelling is correct. Then, click Send. The substance will be added to the list if acceptable otherwise supporting information will be requested. Applicant will be notified through e-mail once the substance has been added.

The actual raw material that is employed in the manufacturing process should 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 the remarks on substance (if any) field [3]
- 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 should 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 substance

Strength of substance: to enter the content of active ingredients (numerical) and then select the weights and measures from the given list.

Note 1: International Non-proprietary Names (INN), approved names, pharmacopoeia names of ingredients should be used whenever possible.

Note 2: Content of ingredients should 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 - 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.)

Note 3: Metric weights and measures shall be used.

Note 4: In cases where product contains active ingredient(s) that cannot be definitely identified, state the name of the material to which activity is ascribed and, where appropriate, the potency or activity of the product.

[3 Remarks on substance (if any) :** This field should be used where the raw material in product formulation yields an equivalent active component.**]

After each ingredient entry is correctly made, click the add 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

Details as for [3] above.

Also to indicate function of substance e.g. sweetener, preservative, etc (select from the display list).

[5] ANY ANIMAL PARTS/MATERIALS

Click the appropriate button (Yes/No).

If yes, please select the animal and its part from the display list.

[6] 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**".]

Click to search from database. For a new manufacturer or if manufacturer is not listed, please click the Not Listed Manufacturer button and fill in the required information. Then, click Send. The details will need to be submitted *upon request (e.g. GMP certificate)* . Applicant will be notified through e-mail once the manufacturer has been added.

Status as to whether the declared manufacturer is a contract manufacturer or otherwise has to be entered.

[7] PRODUCT CLASSIFICATION

Pick one of the following from the list that is displayed:

Scheduled poison
Non-Poison (OTC)
Herbal/Natural Products
Health/Dietary Supplements

Product Import/Marketing Status

Evidence of Products existing in the market before the implementation date should be submitted:
For locally manufactured products: Sales invoice
For imported products: Custom Declaration Form and Sales invoice.

Check List of Product Registration Form Entry for Product Validation

Indicator

T : Herbal/Natural Products
D : Health/Dietary Supplements
X : Non-Poison (OTC)
A : Scheduled Poison
√ : Mandatory
* : Not mandatory
N/A : Not Applicable

Product Validation

Item #	Description	Generic				Innovator
		T	D	X	A	
Item (1)	Product Name	√	√	√	√	√
Item (2)	Dosage Form	√	√	√	√	√
Item (3) –	Active Substance	√	√	√	√	√
Item (4)	Excipient	√	√	√	√	√
Item (5)	Any animal parts used in the product ?	√	√	√	√	√
Item (6)	Manufacturer.	√	√	√	√	√
Item (6)	Is the selected manufacturer a contract manufacturer?.	√	√	√	√	√
Item (7)	Product Classification.	√	√	√	√	√

STEP 2 : REGISTRATION APPLICATION FORM

The application form displayed at Step 2 will depend on the type of product being submitted:

Generic Pharmaceutical Products - Parts I & II.

Herbal/Natural Products/Health Supplements – Parts I & II

Innovator/NCE Products - Parts I to IV.

Part I – Administrative Data and Product Information

Part II – Quality [4]

Part III – Non-clinical

Part IV – Clinical

Please refer to the Glossary developed for the ACTD and ACTR. The definitions used in this 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.

***[**[4] Please refer also to the following guidelines which have been prepared to facilitate submission of relevant documents for PART II (attached as **Annex A**)*

- *Guidelines for submission of protocol of analysis*
- *Guidelines for submission of analytical method validation documents**]***

PART I – ADMINISTRATIVE DATA AND PRODUCT INFORMATION

SECTION A: PRODUCT PARTICULARS

Details of product name, dosage form, formulation (actives and excipients) as entered under Step 1 will appear automatically (**A1, A2, A3**).

Other fields (as follows) will need to be completed.

- ***A4 : Product Description***

State here, briefly, **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.

- ***A5 : Pharmacodynamics & Pharmacokinetics***

Give a concise yet comprehensive summary of the pharmacological profile

A5.1 main and supplementary pharmacological effects (mechanism of action, actions other than the therapeutic effects);

A5.2 relevant pharmacokinetics (absorption, plasma-protein binding, distribution, biotransformation, metabolism, excretion, etc);

A5.3 Environmental properties (for products used directly in the environment e.g. medicines for fish, it may be appropriate to provide general information on environmental effects).

- ***A6 : Indication/Usage***

A6.1 State briefly recommended clinical use(s) of product, indicating clearly also whether curative, palliative, adjunctive, diagnostic, etc.

Note 1: Indications should be specific; phrases such as ‘associated conditions’ or ‘allied diseases’ would not normally be considered appropriate.

Note 2: 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 the prior permission of the DCA.

Note 3: Should it be desired to include new indications, an application shall be filed with the DCA together with supporting clinical documentation on evidence of efficacy and safety for the additional uses (indications).

Note 4: In the case of products which are to be used as dietary supplements, no claims may be made for the prevention and treatment of disease states.

A6.2 State the target species and sub-group, when appropriate.

- ***A7:Recommended Dose & A8:Route of administration***

State the dose (normal dose, dose range) and dosage schedule (frequency, duration) and route of administration appropriate for each therapeutic indication and target species, including direction for proper use of the product by the veterinarian, farmer or owner.
Any special equipment needed for administration of the product should be mentioned. Where the product is to be administered via the feed or water, any dosage adjustment for inappetent animals should be specified, if justified from the data available.

Note 1:Where appropriate, diluents and instructions for dilution, reconstitution and use or administration of the product should be clearly stated.

Note 2: Distinction should be made between therapeutic and prophylactic doses, and between dosages for different clinical uses where applicable.

Note 3: Ensure that dosage recommendation is relevant and appropriate for the product.

Note 4: In the case of premixes for inclusion in the feeding-stuffs: any restriction on the range or type of feed which may be used for the preparation should be indicated. If specific mixing instructions are needed, it should be clearly stated.

- ***A9 : Contraindication***

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

Note 1: Indicate clearly which conditions are absolutely contraindicated, which are contraindicated but under special circumstances may be used and what precautions to be taken in such cases.

Note 2: Where there is likelihood especially for intravenous solutions, that additives are added, foreseeable contraindicated additives should be mentioned.

Note 3: Include also, where possible, concurrent drug therapy which are contraindicated.

- ***A10: Warnings and Precautions***

State briefly precautions and warnings necessary to ensure safe and efficacious use of the drug, including special precautions for use, special warnings for each target species, and special precautions to be taken by the person administering the products to animals.

Where necessary, recommendations to minimise exposure of the product user during administration and, where relevant, during preparation of the product for administration should also be given in this section.

Guidance on remedial action to be taken following accidental contact should also be given, where necessary.

Any measures which can be taken to identify animals at risk and prevent the occurrence, or detect early the onset or worsening of conditions should be stated. If there is a need for awareness of clinical signs representing early warning of a serious ADR, a statement should be included. Any need for specific clinical or laboratory monitoring should be stated.

- ***A11 : Drug Interactions***

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

- products used for the same indication;
- products used for other indications;
- meals, or specific types of food.

- ***A12 : Pregnancy and Lactation***

In order to ensure the safe use of the product, the practitioner must be informed of the recommendations regarding the use of the product in pregnant/lactating animals or laying birds.

The following should be mentioned;

a) conclusions from the animal reproductive toxicity/fertility study;

b) the risk in animals at different times of pregnancy, as assessed from a);

c) information on the possibility of using the product in breeding animals/laying birds.

Use in lactation:

When the active substance(s) or its metabolites are excreted in the milk, a recommendation as to whether to stop or continue to feed (new-born) animals, and the likelihood and degree of adverse reaction should be given.

- ***A13 : Undesirable/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, carcinogenicity, tolerance, liver/kidney toxicity etc.

Indicate also symptoms and sites of effects/reactions. In addition, it should be indicated whether certain species or breeds or types of individual are more susceptible to the undesirable effect concerned, or whether it is more frequent under certain types of husbandry conditions.

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

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

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

- ***A14 : Signs and Symptoms of Overdose and Treatment***

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

- ***A15 : Storage Conditions***

State the recommended storage conditions (temperature, humidity, light etc.).

Storage conditions of reconstituted products should also be included where applicable.
The storage conditions for all the listed pack types should be supported by stability data.

- ***A16 : Shelf Life***

The shelf life for all the listed pack types should be supported by stability data.
A16.1: Shelf-life of the veterinary product as packaged for sale
A16.2: Shelf-life after first opening the container (where relevant)
A16.3: Shelf-life after dilution or reconstitution according to directions (where relevant)

Stability data to support such shelf life should be available.

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

decomposition products are not produced in significant amounts during this period, and that potency, sterility, efficacy of preservative, etc are maintained.

In the case of multi-dose preparations presented in sealed containers, the shelf-life of the broached or opened container should also be stated. Similarly, in the case of premixes for medicated feed, the shelf-life should be indicated for the premix, and for the medicated feed.

- ***A17 : Therapeutic Code***

Applicants should indicate the WHO assigned ATCvet code for each distinct therapeutic indication proposed for a product, if such a code is available. Click to search database.

- ***A18: If the product is for food producing animals***

18.1 ***Withdrawal Period(s)***

The withdrawal period is defined as the period between the last administration of the veterinary product to animals under normal conditions of use and the production of foodstuffs from such animals.

If necessary different withdrawal periods should be stated for meat and offal, milk, eggs and honey. Withdrawal periods should be indicated in days, except for milk withdrawal periods, which may be more appropriately expressed in hours.

A zero withdrawal period should be expressed as *'Zero hours/days'*.

However, for fish meat, the withdrawal period should be stated in degree days. The number of degree days is divided by the average water temperature, in ℃, to give the withdrawal period in days.

Please state the source of reference for information supplied.

18.2 ***Maximum Residual Limit (MRL)***

A Maximum Residual Limit (MRL) is defined as *the maximum concentration of residue resulting from the use of a veterinary medicinal product (expressed in mg/kg or g/kg on a fresh weight basis) which may be accepted to be legally permitted or recognised as acceptable in or on a food.*

In order to protect the health of the consumer of foodstuffs of animal origin, one of the most important principles is that foodstuffs obtained from animals treated with veterinary products must not contain residues of the drug or its metabolites which might constitute a health hazard for the consumer.

Please refer to Appendix 12 to see Allowable Maximum Residual Limit food. For substances not in the list, source of reference for the limit has to be provided.

SECTION B: PRODUCT FORMULA

Batch Manufacturing Formula

Give the 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 will need to be entered.

An **attachment** of the Batch Manufacturing Formula documentation can also be made.

If the product contains or consist of Genetically Modified organism (GMO), please state the ingredient/organism used.

SECTION C : PARTICULARS OF PACKING

To add packing particulars to the listing of packing,

- select pack size (C1) and fill details by weight, or volume or quantity;
- select container type (C2);
- key in Barcode/serial No (C3) (not compulsory);
- key in recommended distributor's price (C4) (not compulsory);
- key in recommended retail price (C5) (not compulsory);

and then click "Add" button

To add next particulars repeat the same process until all the 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

Outer(Carton), Inner & Blister/Strips Labels

The following information should be present on the labeling of the product:

	Parameters	Unit Carton	Inner/ 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.	Expiration Date	✓	✓	✓
8.	Dosage and Administration	✓	✓	NA
9.	Storage Condition	✓	✓*	NA
10.	Country's Registration Number	✓	✓*	NA
11.	Name & Address of Manufacturer	✓	✓*	NA
12.	Name & Adress of Registration Holder	✓	✓*	NA
13.	Warnings/Precautions (if applicable)	✓	✓*	NA
14.	Pack Sizes (unit/volume.)	✓	✓	NA
15.	Direction for Use	✓	✓*	NA
16.	Withdrawal Period (product for food producing animal)	✓	✓*	NA
17.	Name & content of preservative(s) where present	✓	✓	NA
18.	To declare source of ingredients derived from animal origin, including gelatin (active, excipient, and /or capsule shell)	✓	✓*	NA
19.	The words "Keep out of reach of children" or words bearing similar meaning in B.M. and/or English	✓	✓	NA
20.	The words " For animal use only" or words bearing similar meaning	✓	✓	✓
21	The words "This product is registered as a Herbal/Natural Product"; follow by "May be of benefit for improving/ promoting [*organ/system*] health" (for Herbal/Natural products only)	✓	✓	NA
22.	Disposal of containers	✓	✓*	NA
23.	Security Label (hologram)	✓	#	NA
24.	Other specific labelling requirements (if applicable)	✓	✓*	NA
25.	Statement on Controlled Medicines/Ubat Terkawal for product containing Scheduled Poison only	✓	✓*	NA

NA - Not applicable

* Exempted for small labels such as used in ampoules and vials

** For multi-vitamins and minerals preparations it is suggested to label as multi-vitamins and minerals

\# Where inner label is too small, this statement may be printed on the outer label

If the product is without an outer carton, the inner label should bear all the information that is required

Package inserts are required for products classified as Scheduled Poisons. They may also be submitted for OTC products. The draft copy of the package insert should be submitted for evaluation. The following information is required to be included in the package insert:

i) Brand or Product Name
ii) Name and Strength of Active Substance(s)
iii) Product Description
iv) Pharmacodynamics/Pharmacokinetics/Environmental Properties
v) Indication
vi) Recommended Dosage
vii) Mode of Administration
viii) Contraindications
ix) Warnings and Precautions
x) Interactions with Other Medicaments
xi) Statement on usage during pregnancy and lactation
xii) Adverse Effects/Undesirable Effects
xiii) Overdose and Treatment
xiv) Incompatibilities (for injections only)
xv) Withdrawal Period(s)
xvi) Storage Conditions (may be omitted if the information is stated on the label or outer carton labels)
xvii) Dosage Forms and packaging available
xviii) Name and Address of manufacturer/marketing authorisation holder
xix) Date of Revision of Package Insert

Product Information Leaflet can be submitted in place of a package insert for an OTC product. The draft copy of the PIL should be submitted for evaluation. A PIL may also be submitted as additional information for scheduled poison products. The following information is required to be included in the PIL:

i) Name of Product
ii) Description of Product
iii) What is the medicine?
iv) Strength of the medicine
v) What is this medicine used for?
vi) How much and how often should you give this medicine to animal?
vii) When should you not give this medicine to animal?
viii) Undesirable effects/side effects
ix) What other medicine or food should be avoided whilst giving this medicine to animal?
x) What should you do if you miss a dose for the animal?
xi) How should you keep this medicine?
xii) Signs & symptoms of overdose
xiii) What to do when you have given more than the recommended dosage to the animal?
xiv) Name/logo of manufacturer/importer/marketing authorisation holder
xv) Care that should be taken when giving this medicine to animal?
xvi) When should you consult your veterinarian?

SECTIONS E: SUPPLEMENTARY INFORMATION

A) The Summary of Product Characteristics (SPC), if any, Package Insert (PI) and PIL (if any) approved by the country of origin should be submitted with the application.

B) Justification/Rationale for combination products should be submitted in E12.

C) Worldwide registration status is to be listed in E16.

Check List of Product Registration Form Entry for Part 1

Indicator

T : Herbal/Natural Products
D : Health/Dietary Supplements
X : Non-Poison (OTC)
A : Scheduled Poison
√ : Mandatory
* : Not mandatory
N/A : Not Applicable

Section A

Item #	Description	Generic				Innovator
		T	D	X	A	
Item A1	Product Name (As entered in the Product Validation)	√	√	√	√	√
Item A2	Name and Strength of Active Ingredient	√	√	√	√	√
Item A3	Dosage form particulars	√	√	√	√	√
Item A4	Product Description	√	√	√	√	√
Item A5.1	Pharmacodynamics	N/A	N/A	√	√	√
Item A5.2	Pharmacokinetics	N/A	N/A	√	√	√
Item A5.3	Environmental Properties (for product used directly in the environment e.g. medicine for fish)	√	√	√	√	√
Item A6.1	Indication	√	√	√	√	√
Item A6.2	Targeted Species	√	√	√	√	√
Item A7	Recommended Dose	√	√	√	√	√
Item A8	Route Of Administration	√	√	√	√	√
Item A9	Contraindication	√	√	√	√	√
Item A10	Warning and Precaution	√	√	√	√	√
Item A11	- Interaction with Other Medicaments	√	√	√	√	√
Item A12	- Pregnancy and Lactation	N/A	N/A	√	√	√
Item A13	Side Effects	√	√	√	√	√
Item A14	Symptoms and Treatment of Overdose	√	√	√	√	√
Item A15	Storage Condition	√	√	√	√	√
Item A16.1	Shelf Life (as packaged for sale)	√	√	√	√	√
Item A16.2	Shelf Life (after first opening of container, where relevant)	√	√	√	√	√
Item A16.3	Shelf Life (after reconstitution or	√	√	√	√	√

Item #	Description	Generic				Innovator
		T	D	X	A	
	dilution, where relevant)					
Item A17	Therapeutic Code	*		√	√	√
Item A18.1	Withdrawal Period (for food producing animal only)	√	√	√	√	√
Item A18.2	Maximum Residual Limit (MRL) (for food producing animal only)	√	√	√	√	√

Section B

Item #	Description	Generic				Innovator
		T	D	X	A	
Item B1.1	Batch Manufacturing Formula	√	√	√	√	√
	Batch Size	√	√	√	√	√
	Batch Unit	√	√	√	√	√
	Quantity	√	√	√	√	√
	Overage (if any)	*	*	*	*	*
Item B 1.2	Does the product or consists of Genetically Modified Organisms (GMO)? (where relevant)	√	√	√	√	√
Item B 1.3	Attachment of Batch Manufacturing Formula Description	√	√	√	√	√

Section C

Item #	Description	Generic				Innovator
		T	D	X	A	
Item C1	Pack Size	√	√	√	√	√
Item C2	Immediate Container Type	√	√	√	√	√
Item C3	Barcode Serial No	*	*	*	*	*
Item C4	Recommended Distributor Price	*	*	*	*	*
Item C5	Recommended Retail Price	*	*	*	*	*

Section D

Item #	Description	Generic				Innovator
		T	D	X	A	
Item D1.	Label (Mockup) for immediate	√	√	√	√	√
Item D2.	Label (Mockup) for Outer Carton Yes/No	√	√	√	√	√
Item D3	Proposed Package Insert	*	*	√*	√	√

√* : Not mandatory if all information is already in the mock-up label

Section E

Note : Item E4 to E6.3 only applicable for Imported product.

Item #	Description	Generic				Innovator
		T	D	X	A	
Item E1.1.	Product Owner	√	√	√	√	√
Item E1.2.	Letter of Authorization from Product Owner	√	√	√	√	√
Item E2.1.	Letter of Appointment of Contract Manufacturer from Product Owner – For Contract manufacturer Only	√	√	√	√	*
Item E2.2.	Letter of Acceptance from Contract Manufacturer. For Contract manufacturer Only	√	√	√	√	*
Item E3.	Is the Active Substance(s) patented in Malaysia.	N/A	N/A	√	√	√
Item E4.	Certificate of Pharmaceutical Product (CPP)- For Imported product ONLY	√	√	√	√	√
Item E4.1	Certificate of Pharmaceutical Product Issuing Body –For Imported product	√	√	√	√	√

Item #	Description	Generic				Innovator
		T	D	X	A	
	ONLY					
Item E4.2	Is this product license to be placed on the market for use in the exporting country?- For Imported product ONLY	√	√	√	√	√
Item E4.3	Is the product on the market in the exporting country? For Imported product ONLY	√	√	√	√	√
Item E4.4	Date of issue of Certificate of Pharmaceutical Product (CPP))- For Imported product ONLY	√	√	√	√	√
Item E4.5	Date of expiry of Certificate of Pharmaceutical Product (CPP)- For Imported product ONLY	√	√	√	√	√
Item E5.	Certificate of Free Sale (CFS) / Second Certificate of Pharmaceutical (CPP).- For Imported product ONLY if CPP is not available	√	√	√	√	√
Item E5.1	Certificate of Free Sale (CFS) Issuing Body – For Imported product ONLY if CPP is not available	√	√	√	√	√
Item E5.2	Date Of issue of Certificate of free sale (CFS) – For Imported product ONLY if CPP is not available	√	√	√	√	√
Item E5.3	Date Of expiry of Certificate of free sale (CFS)- For	√	√	√	√	√

Item #	Description	Generic				Innovator
		T	D	X	A	
	Imported product ONLY if CPP is not available					
Item E6	Attachment of Good Manufacturing Practice (GMP) For Imported product ONLY if CPP is not available	√	√	√	√	√
Item E6.1.	Certificate of Good Manufacturing Practice (GMP) For Imported product ONLY if CPP is not available	√	√	√	√	√
Item E6.2.	Date of issue of Certificate Good Manufacturing Practice (GMP) For Imported product ONLY if CPP is not available	√	√	√	√	√
Item E6.3.	Date of expiry of Certificate Good Manufacturing Practice (GMP) For Imported product ONLY if CPP is not available	√	√	√	√	√
Item E7.	Summary of Product Characteristics	N/A	N/A	*	*	√
Item E8.	Product Information Leaflet (PIL)	N/A	N/A	*	*	√
Item E9.	Attachment of Analytical Validation	N/A	N/A	*	*	√
Item E10.	Attachment of Protocol Analysis	*	*	√	√	√
Item E11.	Attachment of Certificate Of Analysis (Minimum 2	√	√	√	√	√

Item #	Description	Generic				Innovator
		T	D	X	A	
	Batches)					
Item E12.	Other supporting Document	*	*	*	*	*
Item E13.	Manufacturer Captured from Product Validation (Item 6)	No entry	No entry	No entry	No entry	No entry
Item E13.1	Importer – For Imported product ONLY.	√	√	√	√	√
Item E14	Other Manufacturer(s) Involved? (If any)	√	√	√	√	√
Item E14 (b)	Entry for Processing Type and GMP Certificate	√ (If E14 is Yes)	√ (If E14 is Yes)	√ (If E14 is Yes)	√ (If E14 is Yes)	√ (If E14 I is Yes)
Item E15.	Store Address	*	*	*	*	*
Item E16.	World wide registration status – For Imported product ONLY.	√	√	√	√	√

PART II

Please refer to ASEAN Technical Requirements Guidance Documents listed below:

ASEAN Guideline for Validation of Analytical procedures

ASEAN Guidelines on Process Validation

ASEAN Guideline for Drug Product Stability Study

Glossary of terms used in the ACTD/ACTR

Please also refer to the relevant VICH Guidelines.

For innovator/NCE products, complete documents for Part II (Substance and Product) need to be submitted. For other categories of products, only the indicated documents should be submitted.

Section S

Check List of Product Registration Form Entry for Part S

For GENERIC PRODUCT (T and D), Section S is **Not Applicable**

Item #	Description	Generic				Innovator
		T	D	A	X	
Item S1.1	Nomenclature			√	√	√
Item S1.2	Structure			√	√	√
Item S1.2.1	Attachment For Structure			√	√	√
Item S1.3	General Properties			√	√	√
Item S2.1	Manufacturer Name			√	√	√
Item S2.2	Description of Manufacturing Process and Process Controls			N/A		√
Item S2.3	Controls of Materials			N/A		√
Item S2.4	Controls of Critical Steps and Intermediates			N/A		√
Item S2.5	Process validation and/or Evaluation			N/A		√
Item S2.6	Manufacturing Process Development			N/A		√

Item #	Description	Generic				Innovator
		T	D	A	X	
Item S3.1	Elucidation of Structure and Characteristics			N/A		√
Item S3.2	Impurities			N/A		√
Item S4.1	Specification			√	√	√
Item S4.2	Analytical Procedures			N/A		√
Item S4.3	Validation of Analytical procedure			N/A		√
Item S4.4	Batch Analysis			√	√	√
Item S4.5	Justification of Specification			N/A		√
Item S5	Reference Standards or Materials			N/A		√
Item S6	Container Closure System			N/A		√
Item S7	Stability			*	*	√

Section P

Check List of Product Registration Form Entry for Part P

Note :All fields with the icon are compulsory to be keyed in, except if stated (if any).

Item #	Description	Generic				Innovator
		T	D	X	A	
Item P1	Description and Composition	√		√		√
Item P2.1	Information on Development Studies	N/A		N/A		√
Item P2.2	Components of Drug Product	N/A		N/A		√
Item P2.3	Finished Products	N/A		√		√
Item P2.4	Manufacturing Process Development	N/A		N/A		√
Item P2.5	Container Closure System	N/A		√		√
Item P2.6	Microbiological Attributes	N/A		*		√
Item P2.7	Compatibility	N/A		N/A		√
Item P3.1	Batch Manufacturing Formula	√		√		√
Item P3.2	Manufacturing Process and Process Controls	√		√		√
Item P3.2.1	Manufacturing Process flowchart (attachment)	√		√		√
Item P3.3	Controls of Critical Steps and Intermediates/ IPQC	√		√		√
Item P3.4	Process validation	N/A		*		√

Item #	Description	Generic				Innovator
		T	D	X	A	
	and / or Evaluation					
Item P4.1	Specifications (attachment)	N/A		*		√
Item P4.2	Analytical Procedures	N/A		*		√
Item P4.3	Validation of Analytical Procedures	N/A		*		√
Item P4.4	Justification of Specifications	N/A		N/A		√
Item P4.5	Excipient of Human or Animal Origin	N/A		√		√
Item p.4.6	Novel Excipients	N/A		N/A		√
Item P5.1	Specification	√		√		√
Item P5.2	Analytical Procedures	N/A (for T) * (for D)		√		√
Item P5.3	Validation of Analytical procedure	N/A		*		√
Item P5.4	Batch Analysis (attachment)	√		√		√
Item P5.5	Characterization of Impurities	N/A		N/A		√
Item P5.6	Justification of Specification(s)	N/A		N/A		√
Item P6	Reference Standards or Materials	N/A		N/A		√
Item P7	Container Closure System	N/A		√		√
Item P8	Stability (attachment)	√		√		√
Item P9	Product Interchangeability/ Equivalence evidence	N/A		N/A		√

PART III and PART IV

For innovator/NCE products, complete documents for Part III and Part IV should be submitted immediately after online submission of Part I and II. Please submit the documents in hard copy (printed) as well as soft copy (preferably in CD's) to NPCB.

Part III and IV are adopted and adapted from EMEA Guidelines and APVMA Guidelines. Please also refer to the relevant VICH Guidelines.

PART III: Non Clinical (Safety and Residues Documentation)

III A : SAFETY DOCUMENTATION	
1	**Pharmacology**
	1.1 Pharmacodynamics
	1.2 Pharmacokinetics 1.2.1 Absorption 1.2.2 Distribution 1.2.3 Metabolism (inter-species comparison) 1.2.4 Excretion 1.2.5 Other Pharmacokinetics Studies
2	**Toxicology**
	2.1 Single Dose Toxicity
	2.2 Repeat Dose Toxicity
	2.3 Tolerance in the target species of animal – Target animal safety
	2.4 Reproductive Toxicity *2.4.1 Studies of the effects on reproduction* *2.4.2. Embryotoxicity/foetotoxicity, including tetarogenicity*
	2.5 Mutagenicity
	2.6 Carcinogenicity (if necessary)
3	**Studies of Other effects**
	3.1 Special studies (e.g. neurotoxicity, sensitisation etc.)
	3.2 Microbiological studies
	3.3 Studies on metabolites, impurities, other substances & formulation
4	**User Safety**
	4.1 Inherent toxicity or other harmful effects
	4.2 Route and degree of exposure
	4.3 Risk management proposal
5	**Environmental Risk Assessment (Environmental Safety)**
	5.1 Extent of exposure of the product to the environment
	5.2 Specific investigations of the following, as appropriate : - fate and degradation in soil, fate and behaviour in water and air, effects on aquatic organisms, effects on other non-target organisms
6	**Key Literature**

III B : RESIDUE DOCUMENTATION (Human Food Safety) (For a product intended for use in food-producing animal species)	
1	Formulation used in residue studies
2	**Residue Studies**
	2.1 Pharmacokinetics
	2.2 Depletion of residues
	2.3 MRLs
	2.4 Withdrawal periods
3	**Analytical Method(s)**
	3.1 Description of the method
	3.2 Validation of the method 3.2.1 Specificity 3.2.2 Accuracy, including sensitivity 3.2.3 Precision 3.2.4 Limit of detection 3.2.5 Limit of quantitation 3.2.6 Practicability and applicability under normal laboratory conditions 3.2.7 Susceptibility to interference 3.2.8 Storage stability

PART IV : Clinical (Efficacy Documentation)

Part III and IV are adopted and adapted from EMEA Guidelines and APVMA Guidelines. Please also refer to the relevant VICH Guidelines.

IV A : PRE-CLINICAL DOCUMENTATION	
1	1.1 Pharmacodynamics 1.2 Pharmacokinetics
2	Target Species Tolerance
3	Resistance

IV B : CLINICAL DOCUMENTATION
Summary of the results and critical evaluations of dose determination and dose confirmation studies and clinical trials Tabular presentation of all clinical trials and studies Individual Summary of the most important and significant studies Summary of Clinical Safety etc

ANNEX A

Guidelines for the submission of protocol of analysis

I. General Requirements

1. The Protocol of analysis must be in a standard format that contains information as stated below:-
    a. Product name
    b. Name and address of manufacturer
    c. Name, signature and designation of authorized person
    d. Effective date
    e. Review date

2. Protocol of analysis must consist of all test methods and specifications that are carried out by the manufacturer. Standard pharmacopoeias, for example, BP/USP can be used as references. The tests and specifications in the pharmacopeias are the minimum requirements.

3. Photocopies of methods/ methods directly copied from pharmacopoeias are not acceptable. Manufacturers can use methods from those standard references but must have their own written and detailed procedure.

4. Manufacturers must confirm that all test methods in their protocol of analysis perform as expected. Copies of chromatograms (HPLC/GC/TLC), UV spectrum etc must be submitted together with the protocol of analysis.

5. Protocol of analysis must be properly ordered with proper numbering for all tests and specifications.

6. All references stated in the protocol of analysis must be submitted and clearly labeled.

7. Protocol of analysis submitted must be in either Bahasa Malaysia or English. Protocol of analysis in other languages will be rejected.

8. An authorized copy of latest certificate of analysis for the product concern must be submitted with the protocol of analysis.

II. Specific Requirements

1. Identification test
    a. List of equipment and apparatus required.
    b. List of chemical / reagents
    c. Preparation of sample and standard solutions.
    d. Details of method and procedures.
    e. Specification and acceptance criteria

2. Physical test (friability, uniformity of weight, pH, viscosity, etc).
    a. List of equipment required together with test parameters.
    b. Sample preparation (if any).
    c. Specification and acceptance criteria

3. Disintegration test
    a. Equipment required

b. Test parameters
c. Test medium
d. Specification

4. Dissolution test
   a. Equipment and apparatus required.
   b. List of chemical / reagents required
   c. Test parameters i.e. type and volume of dissolution medium, rotation rate, temperature of solution and time.
   d. Preparation of dissolution medium, preparation of sample and standard solution (if any), etc.
   e. Type and method of analysis (HPLC, UV, etc) and test procedures. For example, if HPLC method is used, test method has to include the preparation of mobile phase, brand and type of column used, run time, detector used (UV, RI, etc), injection volume, system suitability test and other parameters.
   f. Typical chromatograms / UV spectrum for sample & standard solution, system suitability etc.
   g. Complete formula for calculation. For example, 'slow release' products calculation must include quantity of active substance in the medium volume which have been taken out for analysis.
   h. Test specification

5. Impurities / degradation / purity test
   a. List of equipment and apparatus required,
   b. List of chemical and reagents required.
   c. Preparation of sample and standard solutions.
   d. Detailed method and procedures
   e. Complete formula for calculation.
   f. Typical chromatogram of system suitability test, sample & standard solutions if applicable.
   g. Specification / acceptance criteria.

6. Assay and uniformity of content
   a. List of equipment and apparatus required,
   b. List of chemical and reagents required.
   c. Preparation of sample and standard solution
   d. Detailed method and procedures
   e. Complete formula for calculation.
   f. Typical chromatogram/spectrum of system suitability test, sample & standard solutions if applicable.
   g. Specification / acceptance criteria.

7. Pyrogen / abnormal toxicity test
   a. List of equipment, apparatus, glassware and reagents required.
   b. Preparation of sample solution and injection dose.
   c. Test method & procedure.
   d. Test interpretation
   e. Test specification

8. Bacterial Endotoxins Test (LAL)
   a. List of apparatus, glassware and reagents required.
   b. Preparation of standard solution, LAL reagent/substrate and sample.
   c. Determination of MVD (Maximum Valid Dilution) and endotoxin limit.
   d. Detailed test procedure.

e. Calculation and interpretation of test result
f. Test specifications.

9. Microbial Limit Test

9.1 Determination of microbial contamination test
   i. List of apparatus and culture required.
   ii. Preparation of test medium and growth promotion test.
   iii. Sample preparation including method for neutralizing of preservatives for samples that contain preservatives.
   iv. Complete test procedure by 'surface spread' for bacteria and 'pour plate' for fungi.
   v. Colony counting
   vi. Specification and acceptance criteria

9.2 Test for specified microorganisms and total viable aerobic count
   i. List of apparatus and culture required.
   ii. Preparation of test medium and growth promotion test.
   iii. Sample preparation including method for neutralizing of preservatives for samples that contain preservatives.
   iv. Complete test procedure for each of specific microorganism involved.
   v. Observation on colonies presence.
   vi. Specifications and acceptance criteria.

10. Sterility test
   a. List of apparatus required.
   b. List of biological and chemical substance required:-
      i. Culture medium
      ii. List of rinsing solution, buffer solution and diluent
      iii. Neutralizing agent (if any)
      iv. List of specific type cultures required
   c. Method used (e.g. membrane filtration method, direct inoculation, etc)
   d. Method of preparation of the following solutions/materials:-
      i. Culture medium (e.g. Fluid Thioglycollate Medium and Soyabean Casein Digest Medium).
      ii. Rinsing solution, buffer solution and diluents.
      iii. Neutralizing agent (if any).
      iv. Microorganism culture
   e. Growth promotion test for medium used in sterility testing (specific aerobes, anaerobes and fungi).
   f. Preparation of sample solution (including neutralizing procedure of antimicrobial agent for antibiotic samples and samples which contain preservatives).
   g. Complete test procedure for sterility test.
   h. Specifications and acceptance criteria.
   i. Validation procedure & validation data (if applicable).

11. Microbiology assay
   a. List of apparatus required.
   b. List of biological and chemical substances required.
   c. Procedure for the preparation of following solutions/substances:-
      i, Culture mediums
      ii. Rinsing solutions.
      iii. Buffer solutions

iv. Diluents
v. Microorganism culture used in assay

d. Test method (e.g. agar diffusion, turbidimetric, randomized block, dose, etc)
e. Test procedure
   i. Preparations of solutions containing antimicrobial agents which may be present in the sample to be tested (if applicable).
   ii. Preparation of standard solutions (including any steps to counteract the antimicrobial properties of any preservatives, etc present in the sample)
   iii. Preparation of test solutions (including any steps to neutralize the antimicrobial properties of any preservatives, etc present in the sample)
   iv. Dilution schemes for test and standard solutions.
   v. Application of test & standard solutions (volume, latin squares, etc)
   vi. Incubation temperature & time
   vii. Procurement of test data.
f. Complete calculation for the test including ANOVA tablet and other data showing validity of test results.
g. Specifications and acceptance criteria.

Guideline for submission of analytical method validation documents.

1. Introduction

The requirements for the submission of the analytical method validation data and documents by the industry to the Drug Analysis Division, National Pharmaceutical Control Bureau (NPCB) are presented in this guide.

All the analytical validation done by the industry should be in accordance to ASEAN and ICH Technical Requirements Guidance Documents specifically:-

Q2A: Text on validation of analytical procedures, 1994
Q2B: Validation of analytical procedure: methodology, 1996

2. Requirements

The industry is required to submit the following documents for evaluation by NPCB:-

a. Analytical method protocol for the testing of the raw materials (only the active pharmaceutical ingredients (API) and preservatives if any). This should include the specifications and certificate of analysis. All analytical test procedures where possible should be in accordance with the official monograph of that ingredient in the latest edition of the official pharmacopoeia such as British Pharmacopoeia, United States Pharmacopoeia and WHO.

b. Analytical method validation protocol for the finished product. The protocol of analysis should be in accordance with NPCB's guidelines for the submission of protocol of analysis.

c. Protocol for the analytical method validation procedure carried out on the finished product. This procedure should include all details about the validation process including preparation of all solutions used – standards, samples, placebo etc, detection methods, test conditions, equipment used, statistical analysis & evaluation, calculations etc.

Types of analytical procedures to be validated includes:-
i. Identification tests
ii. Quantitative tests for impurities' content
iii. Limit tests for control of impurities
iv. Quantitative tests of the active ingredient in the sample
v. Pyrogen / Bacterial endotoxin test
vi. Sterility test

A brief description of the type of tests considered in this document is provided below:-

Identification tests are intended to ensure the identity of an active ingredient in the sample. This is normally achieved by comparison of a property of the sample e.g. spectrum, chromatographic behavior, chemical reactivity, etc) to that of a reference standard.

Testing for impurities can be either a quantitative test or a limit test for the impurity in the sample. Either test is intended to accurately reflect the purity characteristics

of the sample. Different validation characteristics are required for a quantitative test than for a limit test.
Assay procedures are intended to measure the content of active pharmaceutical ingredient present in a given sample. The analytical data submitted must be able to support the claim that the analytical method employed has been validated.

Pyrogen Test and Limulus Amebocyte Lysate Test - Relevant validation data for pyrogen test and Limulus Amebocyte Lysate Test include product independent data such as equipment validation, validation of temperature system, lysate sensitivity and product dependent validation data such as inhibition / enhancement studies and validation for routine LAL tests according to the type of LAL test method employed eg. Gel Clot method, quantitative end point method or quantitative kinetic method.

Sterility testing applied to products that are required to be sterile. A satisfactory result indicates that no contaminating microorganism has been found in the sample examined in the condition of the test. For sterility testing it is imperative that the testing procedure adopted by the manufacturers include all aspects of validation of the testing method including the precautions against microbial contamination.

d. Complete set of data obtained from the validation process. These include all raw data such as weights used, chromatograms, tabulated sets of value as well as graphs, statistical analysis & evaluation, calculations & formulae etc. Summary of data will not be accepted. Acceptance criteria for each characteristic/ parameter should also be submitted. For products tested using analytical methods described in official pharmacopeias, users are not required to validate accuracy and reliability of these methods, but must submit data verifying their suitability under actual conditions of use.

e. Certificate of analysis of three (3) recent batches of the finished product.

f. Certificate of analysis for one batch of API used in the product.

g. Summary on the validation process together with conclusion reached.