# PART II

# GUIDELINES FOR VETERINARY MEDICINAL PRODUCTS REGISTRATION IN PALESTINE

# Table of Content

# 1. Introduction:

The policy of the Ministry of Health aims at ensuring that all drugs manufactured, imported or exported, distributed or sold in Palestine are of good quality, safety and efficacy, the process of drug registration forms an important basis for evaluating and assuring drug safety, efficacy and quality.

These guidelines are intended to give the Department of Drug Control and Registration (DDCR) the requirements for documentation and assembling of applications for registration of veterinary products in Palestine.

They prescribe the format and content of registration file, labeling and package insert information requirements, guidelines on stability study requirements, amendments and changes requirements and renewal of registration requirements.

The implementation of these guidelines includes veterinary products, including premixes, dietary/health supplements or herbal preparations intended to be administered to animals for medicinal purpose.

Dietary/health supplements are taken orally in the forms such as pills, capsules, tablets, liquids or powder and not represented as a conventional food item for a meal or diet.

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

A veterinary drug product will be registered only if it satisfies all requirements of registration, especially with respect to safety, efficacy and quality of the product. Other criteria that may be taken into consideration include:

- Whether the product is needed or not. Factors like potential for abuse, number of registered products, different dosage form, etc are considered.
- Therapeutic advantage.

## 2. Definitions:

For the purpose of these guidelines, the following definitions shall apply:

1. **Active pharmaceutical ingredient (API):**
   Means a substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).
2. **Composition:**
   Composition in relation to a medicinal product means the ingredients of which it consists, proportions, degree of strength, quality and purity in which those ingredients are contained.
3. **Container:**
   Means a bottle, jar, box, packet, sachet or other receptacle which contains or is to contain in it, not being a capsule or other article in which the product is or is to be administered or consumed, and where any such receptacle is or is to be contained in another receptacle, includes the former but does not include the latter receptacle.
4. **Container labelling**
   Means all information that appears on any part of a container, including that on any outer packaging such as a carton.
5. **Drug, medicine or pharmaceutical product:**
   Means any substance or mixture of substances manufactured sold or represented for use in:
   a. The diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical or mental state, or the symptoms thereof, in an animal;
   b. Restoring, correcting or beneficial modification of organic or mental functions in an animal;
   c. Articles intended for use as a component of any articles specified in clause (a), (b) or (c); but does not include medical devices or their components, parts or accessories.

6. **Excipient**

   Means any component of a finished dosage form which has no therapeutic value.

7. **Finished product**

   Means a product that has undergone all stages of production, including packaging in its final container and labeling.

8. **Formulation**

   Means the composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

9. **Generic products**

   Means products that are pharmaceutical equivalents or alternatives to innovator or reference products and which are intended to be therapeutically equivalent and can therefore be used interchangeably with the innovator or reference product.

10. **Innovator (or pioneer) pharmaceutical product**

    Means a pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to the requirements at the time of authorization).

11. **Label**

    Means any tag, brand, mark, pictorial or other descriptive matter, written, printed, stenciled, marked, embossed or impressed on or attached to a container of any drug.

12. **Manufacture**

    Means production, quality control, release and packaging of a product.

13. **Manufacturer**

    Means a person or firm that is engaged in the manufacture of products.

14. **New combination**

    Means a product containing drugs in combinations (qualitative content and/or proportions) different from those products that are subject of current pharmacopoeias.

**15. New active pharmaceutical ingredient**

Means a drug (active ingredient), including its salts, esters, derivatives, etc. or biological agent, which is not a subject of current pharmacopoeias.

**16. Pharmacopoeia**

Means a current edition of the British Pharmacopoeia, European Pharmacopoeia,United States Pharmacopoeia, International Pharmacopoeia and Japanese Pharmacopoeia.

**17. Pharmaceutical alternatives**

Two or more medicinal products are said to be pharmaceutical alternatives if they contain the same active ingredients, but which may differ in salt, esters, dosage forms, strength and/ or route of administration.

**18. Pharmaceutical equivalents**

Products are pharmaceutical equivalents means products that contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standard; and if they are intended to be administered by the same route.

**19. Specification - release**

Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a drug product is suitable for release at the time of its manufacture.

**20. Therapeutic equivalence**

Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or in vitro studies.

# 3. General Registration Provisions:

1. Any pharmaceutical product of any dosage form intended to be used on humans or animals, whether internally or externally, is required to be registered with the Department of Drug Control and Registration (DDCR).
2. All required applications and file documents shall be submitted in original hard copies. Authenticated copies may be accepted if submitted with a clear statement from the original owner allowing the use of the copied documents.
3. All information and documents must be in English/Arabic and legible. Where documents are not originally in English/Arabic, a copy in the original language and a full legalized translation should be submitted.
4. All application forms shall be filled by a competent qualified person (i.e. responsible pharmacist). He or she shall ensure that all information provided to the department (DDCR) is true and correct to the best of his/her knowledge. The applicant shall be aware that if he/she makes any false statement, representation or declaration in connection with an application to the DDCR, he/she shall be guilty of an offence.
5. All the registration conditions and requirements shall be fulfilled by the applicant. If the applicant wishes to waive any condition, he/she shall apply for a waiver together with supporting documents.
6. Authentication (or legalization) of documents, wherever required, shall be done by the relevant health authority, the Ministry of Foreign Sffairs and the Palestinian embassy in the country where the document was issued.
7. The applicants should notify the DDCR of any change in the particulars submitted in the application and of any new significant information during the course of evaluation and as long as the product remains on the Palestinian market.
8. The marketing authorization holder shall notify the department if the product is no longer registered by another country, as long as the product remains on the Palestinian market.

9. The marketing authorization holder shall ensure that the product will be sold, supplied and recommended for use in accordance with the approved and in compliance with all license conditions, applicable legislation and guidelines.
10. Product registration shall be only through authorized agent, exclusive distributor, scientific office or local manufacturer.
11. The registration documents shall be submitted in bounded files, pages shall be numbered and the file should have a protruding dividers, each bearing the name of the relevant section.
12. The registration of a product shall be valid for five years or such period as specified in the registration certificate (unless sooner suspended or cancelled by the DDCR).
13. Renewal of product registration can be done six months prior to the expiry of the validity period of the product registration.
14. Application for renewal of registration shall be submitted to the department not later than four months prior to the expiry of the validity of registration.
15. Upon expiry of the validity period of registration, the renewal of product registration will no longer be accessible and an application for new registration of product can be submitted.
16. The DDCR shall reject, cancel or suspend the registration of any product, if there are deficiencies in safety, quality or efficacy of the product or failure to comply with the conditions of registration.
17. Any applicant or marketing authorization holder aggrieved by the decisions of the DDCR may make a written appeal to the head of the department. All appeals must be made within thirty days of the date of the DDCR notification. The director of the DDCR department shall submit the appeal and the supporting data or documents to the Drug Technical Committee. The decision of the DTC made on any appeal is final.
18. Every application for registration and renewal of registration shall be accompanied by the registration fees, which is to be determined by the Minister of Health.

19. The DDCR will charge the applicant any costs for carrying out laboratory testing relating to the registration or renewal of the registration of any product.
20. Any payment made is not refundable once an application has been submitted and payment confirmed.
21. Letters of authorization and certifications should be valid and current at the time of submission.
22. Where a product is contract manufactured, letters of authorization of contract manufacturer and acceptance to register from the manufacturer and each sub-contractor, if applicable (e.g. repacker).
23. The letter of authorization should be on the product owner's original letterhead and be dated and signed by the managing director, president, or equivalent person who has overall responsibility for the company organization.
24. The letter of acceptance from the manufacturer shall comply with similar requirements as stated above.
25. The letters of authorization and acceptance should state the name of the product(s) concerned and the name and actual site address of the manufacturer(s) involved in the manufacturing of the product(s).
26. A separate application is required for each product i.e. products containing the same ingredient(s) but made to different specification (in terms of strength/content of ingredient(s), dosage form, description, etc) or by a different manufacturer shall require separate applications for product registration.
27. Different primary packing (materials) or pack sizes (quantity or volume) of a product 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 packing and pack sizes stated in the registration documents only.
28. An application for a second source shall be considered where deemed necessary. This second source product shall be the same as the first product in all aspects except for the site of manufacturing.

29. A decision on the approval or rejection of an application shall be made based on the outcome of the evaluation of the submitted documentation. the decision will be sent to the marketing authorizations holder by the DDCR within the stipulated time as stated in the DDCR notification.
30. A registration number will be given when a product application is found to have satisfied the registration requirements of quality, safety and efficacy and is granted registration approval by the DDCR. The registration number is specific for the products registered with the name identity, composition, characteristic, origin (manufacturer) and marketing authorization holder as specified in the registration documents. It must not be used for any other product.
31. A certificate of registration with the provisions, conditions, limitations etc of the registration, shall be issued for the registered product.
32. No change in product name, product specifications, packaging, indications, contents of product label, package insert, or product literature, or any relevant particular of the registered product shall be made without the prior approval of the DDCR. Similarly, prior approval of the DDCR is required for changes in excepients, such as change in lubricant, preservative, solvent 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 products specifications, certificate of analysis, stability data, raw materials specifications, etc should be updated accordingly. The registration of the products may be cancelled if changes are made without prior approval of the DDCR.
33. All necessary documents in accordance to the specified conditions laid for each type of variation (amendment) should be submitted. 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.(Please refer to ***Appendix (1)*** for details of the types of variations allowed and the

conditions and/or supporting documents necessary for each type of variation defined.)

34. Any change, which affects the composition or characteristics of the products such as, colour/ shade, flavour/ fragrance, shape, change of vehicle shall require a new application for registration.
35. The product marketing authorization holder should inform the DDCR of any adverse reaction to the product.
36. The product registration can be cancelled if the marketing authorization holder fails to inform the DDCR of any serious adverse reactions upon receipt of such reports.
37. All labels and package insert must be amended to include any new adverse reactions, warnings, precaution etc.
38. Samples of products registered by the DDCR may be taken and tested for compliance with official pharmacopoeial standards or specifications agreed by the manufacturer.
39. If a sample fails to meet adequate specifications, the marketing authorization holder will be issued a warning. Unless the failure is serious enough to justify recall of the product, the marketing authorization holder has up to thirty (30) days to identify the source/cause of quality defect and actions to be taken to improve quality.
40. The marketing authorization holder should notify the DDCR of any product quality related problems (with registered products) that the holder is aware of. It is also the responsibility of the prescribers, the pharmacists, as well as other health professionals who come into contact with the product to report.
41. The marketing authorization holder is responsible for conducting recalls of defective or unsafe products. It is also his responsibility to notify the DDCR of any recall decision. No recall should take place without first consulting/informing the DDCR.
42. The marketing authorization holder shall inform the DDCR of any decision to terminate the registration of a product before the end of the validity of

such registration. The marketing authorization holder must return the product registration certificate immediately to the DDCR.

43. The registration of a product once terminated shall not be reregistered A new application must be submitted .
44. A product registration (marketing authorization) may be transferred from the existing product marketing authorization holder (MAH) to another holder using a transfer procedure. See ***Appendix (2)*** for this purpose.
45. The DDCR well register a product for any marketing authorization holder only once for the same active ingredient(s).
46. A product will be registered only if it satisfies all requirements of the DDCR, especially with respect to safety, efficacy and quality of the product. other criteria that may be taken into consideration include:
    - Either that the product is needed or not. Aspects like potential for abuse, number of registered products, different dosage form, products containing forbidden excipients, etc are considered.
    - Therapeutic advantage.
47. The DDCR may register locally manufactured products for export only that is to be sold in a different colour (formulation), shape and strength.
48. 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 where by the applicant need only declare to the DDCR the differences in the product for export compared to the registered product marketed in Palestine (such as a product being exported under a different name).A Free Sale Certificate(FSC)/ a Certificate of a Pharmaceutical Product (CPP) will be issued to the applicant for the registered product together with an explanation of any difference(s) to the importing country.
49. Products which are packed together in combination for a therapeutic regimen (example for the treatment of helicobacter pylori, hepatitis C, etc) will be classified as a combination pack. Product shall be registered as a single product.

50. A product which is packed together with diluent(s) is not considered as combination pack product.
51. Combination pack product must consist of registered products only.
52. The use of halal and certification logos (i.e. ISO, GMP. etc) on the labels of drug products will not be allowed.
53. However use of the mentioned logos will be considered for traditional products, food supplements, and also cosmetics, for both local and export market, provided that such products have been certified and approved as halal or ISO or GMP by the DDCR. The use of the logos is based on application to DDCR and is not a mandatory requirement.
54. All the registration data submitted to the DDCR shall be considered confidential and shall be kept in safe manner.

# 4. General Information:

3.1. These guidelines apply to all Veterinary Medicinal Products (VMPs) except biological products, traditional medicinal products, diagnostic aids, medical appliances and public health chemicals.

3.2. All documents are to be submitted typewritten or computer printed in Arabic or English. Where originals are in another language, copies shall be presented together with certified English translations.

3.3. A separate application is required for each product. Products differing in active ingredient(s), strength, dosage forms, package size (preparations for injection only) or manufactured at different sites are considered to be different products and hence require separate applications.

3.4. However pharmaceutically equivalent products bearing the same proprietary name and manufactured at the same manufacturing site, but differing only in packaging material or pack sizes require only one application.

3.5. A pre-approval application for registration is required to be submitted to the "DDCR" for approval purposes before proceeding in the application for registration.

3.6. Application for registration is required to be submitted to the "DDCR" in six copies. The application must be accompanied by:

i) A non-refundable registration fee.

ii) Hard copy of the medicinal product registration file containing prescribed information and all other parts of the file each part shall be signed by authorized persons.

3.7. Application for a quality control certificate shall be submitted to the "DDCR" in two copies. The application must be accompanied by:

i) Samples of finished product in its final pack, in a quantity sufficient for three analyses.

ii) A certificate of analysis for the product from the manufacturer.

iii) Referrence standard materials, accompanied with a certificate of analysis.

iv) Copies from the method(s) of analysis of the product (chemical, physical, biological) as required.

3.8. All ingredients used in the formulation of generic medicinal products must comply with specifications prescribed either in the United States, British, European, International or Japanese pharmacopoeia. In-house specifications shall only be accepted if the limits are tighter than those prescribed in these pharmacopoeias.

3.9. Application for the registration of a veterinary medicinal product shall be made only by the responsible person of:

i) A local manufacturer.

ii) A licensed drug store (wholesaler), who is authorized by drug product owner.

iii) A licensed veterinary drugs store, who is authorized by product owner.

3.10. Complete information shall be submitted on the drug manufacturer. Where different activities of a given product are carried out at different manufacturing sites, the information shall be provided for each site and the activity carried out at the particular site shall be stated.

3.11. Dosage form shall mean the form in which the drug is presented, e.g. solution, suspension, eye drops, emulsion, ointment, suppository, tablet, capsue,etc. for injections, the type of presentation (e.g. vial, ampoule, dental cartridge, etc), and the type of content (e.g. powder for reconstitution, solution, suspension, oily solution, etc) shall also be stated.

3.12. Storage conditions shall be stated in actual humidity and temperature range as shown below:

3.12.1. Store under normal storage conditions ($15^{o}C$ – $30^{o}C$).

3.12.2. Store between $2^{o}C$ – $8^{o}C$ (refrigeration, no freezing).

3.12.3. Store below $8^{o}C$ (refrigeration).

3.12.4. Store betweem $-5^{o}C$ – $0^{o}C$ (in a freezer).

3.12.5. Store below -18$^{o}$C (in a deep freezer)

3.13. <u>For imported veterinary medicinal products the following shall be submitted:</u>

3.13.1 The valid licence for the drug store/wholesaler or scientific office issued from the Ministry of Health.

3.13.2. A legalized letter of appointment from the owner of the medicinal product, showing that the importing company is the sole agent/exclusive distributer. The letter should be authenticated by the Palestinian embassy in the country of origin.

3.13.3 An authorization for registration from the product owner.

3.13.4 An authenticated certificate of pharmaceutical product (CPP) or free sale certificate(FSC) issued from the responsible health authorities of the producer`s country of origin.

3.13.5 A valid GMP certificate issued from the responsible health authorities of the producer`s country of origin.

3.13.6 All the above mentioned document should be authenticated by the Palestinian embassy in the country of origin.

3.13.7 The site master file of the producing company. ***See Appendix (3)***

# 5. Contents of chemical and pharmaceutical data

The material shall be submitted in a hard cover file. The following shall appear on the outside of the file: **name of the medicinal product**, **dosage form**, **strength and name of the manufacturer & name of the agent (for imported veterinary medicinal products)** the file shall have a protruding dividers, each bearing the name of the relevant section.

## Documents required to be in the registration file:

1. **Table of content.**

2. **The complete and accurate composition of the product, active and inactive ingredients whether they appear in the final product or not:**

   2.1. Quantities should be in unit per dose.

   2.2. The composition should be formatted as below:

| Name of Ingredients | Unit & or percentage Formula | Function | Reference to Standard |
|---|---|---|---|
| Active substance(s) | | | |
| Inactive Substances | | | |

   2.3. Should be approved by the concerned department in the M.O.H of the country of origin (for imported drugs)

3. **Development of products:**
   Explanation with regard to the choice of formulation, composition, ingredients and container closure systems. Supported, if necessary, by data on development pharmaceutics. The overage, with justification thereof, should be stated. Tests carried out during pharmaceutical development must be described in detail (e.g. in vitro dissolution studies for solid pharmaceutical forms).

## 4. Chemistry, manufacturing and quality control data:

### 4.1. Monographs of the active ingredients which must have the following information:

The International Non-propriety Name (I.N.N).

- Description of the active material.
- Chemical & physical & microbiological (where applicable) specification.
- Methods of analysis.
- Structural formula & molecular weight.
- Source of supply including the name & address of the site of the manufacturer.
- Purity tests.
- Impurities.
- Identification tests.
- Copy of the pharmacopoeial reference.
- Certificate of analysis from the manufacturer.
- Drug master file (DMF) for non-pharmacopoeial materials.

### 4.2. Monographs of the inactive ingredient which must have the following information:

- International non-propriety name (I.N.N).
- Specifications.
- Method of analysis.
- Structural formula
- Source of supply including the name and the address of the site of the manufacturer.
- Photocopy of the pharmacopoeial reference.
- Certificate of analysis from the manufacturer.

### 4.3. Method of preparation:

The document shall include the following:

4.3.1. **Description of the product**:

A concise description of the product should be presented here. These should include; physical characteristics, consistence of the product, shape, size, colour, odour, taste, type liquids should be clearly stated if it is emulsion, elixir, suspension etc.

4.3.2. **Composition of the product**

The composition of the product should be set out under the following topics:

i) Active ingredients and their quantities in:

a. per unit dose
b. percentage composition (w/w, w/v, v/v)
c. weight per ml or
d. quantity per measured dose

INN or approved names or pharmacopoeia names should be used.

4.3.3**. Complete manufacturing master formula**:

Give the actual batch manufacturing master formula with names and quantities of ingredients with the reasons for inclusion (Active and otherwise). Substances which are removed in the course of manufacture should be included. Yield and acceptable limits must be included.

4.3.4. **Overage**:

Where an overage is included, give here the name of the ingredient and amount i.e.

a. quantity per unit dose;
b. % age composition (w/w, w/v, v/v etc).

Reasons for inclusions of overage should be clearly stated i.e. to cover losses during manufacturing etc.

4.3.5. **Manufacturing processes**

All stages involved in the manufacture of the dosage form should be described. Basic principles involved should be clearly set out:

All steps involved and their operations should be carefully described including the conditions subjected to each operation i.e. temperature, pH adjustments, processing time etc. All the details should be made clear and sequenced to the logic. Flow charts would be useful.

**4.4. Packaging procedure**:

A brief description of how the product is packaged into final immediate and outer containers should be given. All stages should be illustrated i.e. filling, weight checking, labelling, packing in hardboard and sealing. Steps, equipment, flow and precautions for each packaging stage be included.

**4.5. In-process control**:

The documents must include:

- All tests which are required to assure the quality in every stage of the drug manufacturing, should be clearly stated with all the permissible limits.

**4.6. Finished product specifications**

Summarized specifications of the final product shall be given, i.e. the acceptable limits of the entire physical, chemical, biological and (where applicable) microbiological parameters. A full description of analytical and other control procedures carried out to ascertain the final product specifications stated above should be given.

Where analytical procedures in various parts of the application coincide, these procedures may be described fully in one part and may be subsequently referred to in other parts, provided that the relevant page and paragraph are clearly identified.

- For pharmacopoeial finished products, photocopies of the relevant monographs may be provided.
- For pharmacopoeial finished products where the methods of analysis used are non-pharmacopoeial, detailed analytical validation of such methods shall be provided. However, the limits used should not be inferior to the Pharmacopoeial limits.
- Following are the details of the data to be supplied. Parameters marked with asterisk are also to be tested within the framework of the stability studies:

**A- Tablets and caplets:**

- Content of the active ingredient per unit dose, including permissible deviation range.*
- Description (shape, imprint).
- Odor (where applicable).*
- Colour (where applicable).*
- Weight of tablet (nominal weight), including permissible deviation range.
- Uniformity of content (where applicable).
- Uniformity of weight.
- Diameter, including permissible deviation range.
- Hardness (where applicable).*
- Thickness, including permissible deviation range.
- Friability.*
- Disintegration.
- Dissolution- including the method of determination with permitted limits.*
- Finesse of dispersion (for dispersible tablet)
- Shelf-life.

**B- Capsules:**

- Content of the active ingredient per unit dose, including permissible deviation range.*
- Type & size of capsule.
- Description, including the contents and capsules imprint (if present).*
- Colour of the cap, body and contents.*
- Fill weight, including permissible deviation range.
- Uniformity of weight.
- Uniformity of content (where applicable).
- Disintegration.*
- Dissolution- including the method of determinationwith permitted limits.*
- Shelf life.

**C- Injections ( solutions and suspension):**

- Content of the active ingredient/s, including permissible deviation range.*
- Colour.*
- Clarity- for solution only.*
- Fill volume, including permissible deviation range.
- pH.*
- Sterility test.*
- Test for pyrogens (for volumes more than 10ml), including test method/ Limulus. Amebocyte test (LAL) for endotoxixs.
- Test for particulate matter- for solution only, including test method.*
- Content of preservative material(s) (if present)*.
- Preservative efficacy test for aqueous injection containing an antimicrobial preservative and intended for multiple dose use.*
- Shelf life.

**D- Dry powder intended for injection immediately following reconstitution:**

- Content of the active ingredient/s, including permissible deviation range.*
- Average weight of content.
- pH after reconstitution.*
- Colour.*
- Odor.*
- Particle size following reconstitution with the diluent-for suspension only.
- Sterility test.*
- Uniformity of weight.
- Uniformity of content (where applicable).
- Test for pyrogens (for volumes more than 10ml), including test method/ Limulus Amebocyte test (LAL) for endotoxixs.
- Data for the diluent ( if supplied), as detailed for injections.
- Shelf life.

**E- Powders**

- Content of the active ingredient/s per pack and per measured dose including permissible deviation range.*
- Average weight.*
- Colour.*
- Odor.*
- Taste (for oral use).*
- Uniformity mass.
- Uniformity of content (where applicable)
- Contamination test (where applicable)
- Particle size ( where applicable)
- Water content.*
- Tapped density.*
- Shelf life.

**F- Solutions including (Syrups & Elixir).**

- Full Details of composition, including inactive ingredient/s.
- Content of the active ingredient/s per unit dose, including permission deviation range.*
- Colour.*
- Odor.*
- Taste.*
- Clarity.*
- Uniformity of content (where applicable)
- Deliverable mass or volume
- Viscosity.*
- pH ( where applicable).*
- Average filling volume/ filling weight.
- Content of preservative material(s) (if Present).*
- Preservative efficacy test.
- Alcohol content with limitations (If applicable give the method in details)
- Shelf life.

**G- Dry powder intended for dissolution but not for use by injection.**

- Data shall be submitted for the powder (as per section E) and tests required for solution after dissolution are (as per section F).

**H- Dry powder intended for suspension but not for use by injection.**

- Data shall be submitted for the powder (as per section E) and for the suspension obtained (as per section I).
- Uniformity of content (where applicable)

**I- Emulsions, Lotions and suspensions:**

- Full details of composition, including inactive ingredient/s.
- Content of the active ingredient/s including permissible deviation range.*
- Colour.*
- Taste (for oral use).*
- Odor.*
- pH.*
- Particle size (rate of particle sedimentation and redispersion of the suspension- for suspensions only).*
- Average filling volume/weight
- Deliverable volume
- Shelf life.

**J- Suppositories and ovules:**

- Content of the active ingredient/s per unit dose, including permissible deviation range.*
- Dimensions.*
- Shape.*
- Colour.*
- Uniformity of mass.
- Uniformity of content (where applicable)

- Dissolution (where applicable).*
- Weight, including permissible deviation range.
- Melting point.*
- Disintegration time, with method of determination.
- Uniformity of content (where applicable).
- Shelf life.

**K- Aerosols (suspension, solution and powders):**

- Content of the active ingredient/s and per measured dose, including permissible deviation range.*
- Description of container and valve, including data on the quantity delivered per actuation.
- Particle size-for powder and suspension only.*
- Uniformity of contents
- Leak test.
- Pressure measurement.
- Shelf life.

**L- Ointments creams and other semi-solid medicinal products:**

- Content of the active ingredient/s per gram of the medicinal product, including permissible deviation range.*
- Average filling weight including permissible deviation range.
- Colour.*
- Deliverable mass or Volume
- Odor.*
- Viscosity. *
- pH.*
- Particle size determination with limits.
- Melting range.*
- Sterility (where applicable).*
- Shelf life.

**M- Eye ear and nose drops:**

- Full details of composition, including inactive ingredient/s.
- Content of the active ingredient/s including permissible deviation range.*
- Colour.*
- Odor.*
- Density
- Delivered mass or volume
- Uniformity of content for products in suspension or emulsions forms
- Uniformity of delivered dose (for metered dose nasal spray).
- Average filling volume.
- Sterility (where applicable).
- Clarity- for solution only.
- Particle size – for suspension only.
- Content of preservative material(s) (if Present)*
- Preservative efficacy test – for aqueous preparation only.*
- pH.*
- Viscosity.*
- Shelf life.

**N- Transdermal medicinal products:**

- Content of the active ingredients/s per patch, including permissible deviation range
- Components of the patch.
- Rate of release of the active ingredient.*
- Colour.*
- Shape.*
- Dimension.
- Dynamic sheer resistance.*
- Adhesive properties.*
- Peeling strength.*
- Uniformity of content
- Dissolution.
- Microbial test.
- Shelf life.

**4.7. Quality control of the finished product**

The quality control method shall include the following:

- Identification tests
- Physical, chemical and, where appropriate, biological and microbiological methods.
- Determination of the anti-microbial or chemical preservative (with limits).
- Photocopy of the monograph should be attached, including the name of the pharmacopoeia used and the edition.
- Analytical validation methods for non-pharmacopoeial methods.

**4.8. Certificate of analysis for the finished product**:

A certificate of analysis for the finished product with all results of the tests as mentioned in the Pharmacotechnical data for that specific form, should be included. The Certificate must be signed and dated by the analyzer and the Quality Control laboratory manager.

**4.9. Stability Study:**

4.9.1. The study shall be carried out on the medicinal product, which is manufactured at the site defined in the application.
Stability studies are carried out to provide information necessary for predicting problems likely to be encountered during storage, establishing storage conditions and establishing a shelf life for the drug.
Following are some general requirements for stability study testing.

4.9.2. Stability studies should investigate:

4.9.2.1. The stability of the drug in unopened packs.

4.9.2.2. Stability of the drug following manipulation necessary prior to administration (e.g. reconstitution or dilution).

4.9.2.3. Stability of the drug during use (e.g. the effects of opening and closing of the container closure system)

4.9.3. The packaging used during stability studies should be the one intended for marketing, in all respects including the relative size.

4.9.4. Both accelerated and realtime stability studies should be carried out in at least three(s) batches. The batch number, date of manufacture and the size of each batch should be mentioned in the study report.

4.9.5. All methods of analysis for stability testing should be fully described, validated, and all analytical methods used to determine degradation products should be submitted. The results of the degradation testing should be submitted.

4.9.6. Date should be presented in a summarized, legible form. Where possible tables and graphs shoul be used. Statistical analysis may be used where appropriate at specified confidence limits.

4.9.7. Results should be discussed and a conclusion (shelf-life) drawn from the studies. Differences within and between batches should be explained. The effects of the storage at temperature and the inferred shelf-life should be summarised.

4.9.8. Shelf-life prediction should be based on available data.

4.9.9. Medicinal products containing preservatives shall undergo microbiological testing at the expiry date of the medicinal product, in order to establish the efficacy of the preservative. The preservative shall be chemically tested during the stability-testing period.

4.10. General storage conditions: the required storage conditions for accelerated and real time stability studies are as follows:

4.10.1. General case

| Study | Storage condition | Minimum time period covered by data at submission |
|---|---|---|
| Long term* | 25°C ± 2°C/60% RH ± 5% RH<br>or<br>30°C ± 2°C/65% RH ± 5% RH | 12 months |
| Intermediate** | 30°C ± 2°C/65% RH ± 5% RH | 6 months |
| Accelerated | 40°C ± 2°C/75% RH ± 5% RH | 6 months |

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

**If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

4.10.2.Drug products packaged in semi-permeable containers:

| Study | Storage condition | Minimum time period covered by data at submission |
|---|---|---|
| Long term* | 25°C ± 2°C/40% RH ± 5% RH<br>or<br>30°C ± 2°C/35% RH ± 5% RH | 12 months |
| Intermediate** | 30°C ± 2°C/65% RH ± 5% RH | 6 months |
| Accelerated | 40°C ± 2°C/not more than (NMT) 25% RH | 6 months |

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.

**If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

4.10.3.Drug substances intended for storage in a refrigerator:

| Study | Storage condition | Minimum time period covered by data at submission |
|---|---|---|
| Long term | 5°C ± 3°C | 12 months |
| Accelerated | 25°C ± 2°C/60% RH ± 5% RH | 6 months |

4.10.4.Drug substances intended for storage in a freezer :

| Study | Storage condition | Minimum time period covered by data at submission |
|---|---|---|
| Long term | - 20°C ± 5°C | 12 months |

4.10.5.Extension of shelf-life: Where studies have not been carried out on full-scale production batches, on-going studies shall be required to substantiate shelf life extension:

4.10.5.1. The shelf-life may be extended on the basis of real-time stability studies carried out for the full shelf-life period.

4.10.5.2. An extension shall never be based on acceberated studies.

4.10.5.3. The shelf-life of a product may not exceed five (5) years.

4.10.6.Stability indicating properties: are properties included in finished product specification which are marked by astrik and any other properties which happen to be stability indicating, including the following:

4.10.6.1. Chemical stability of the active ingredient and any essential excipients (e.g. preservatives and antioxidants).

4.10.6.2. Degradation product(s) levels.

4.10.6.3. Physical properties (e.g. particle size, dissolution, hardness, viscosity, re-suspendability, …etc).

4.10.6.4. Packaging interactions and integrity.

4.10.6.5. Microbiological stability (including anti-microbial preservative efficacy).

4.10.6.6. Organoleptic properties (odour, taste, ..etc).

4.10.7. The detailed requirements of stability study testing and report are outlined in ICH guidelines ( ICH Q1A (R2), ICH Q1B, ICH Q1C, ICH Q1D, ICH Q1E, ICH Q3A)

The applicant is required to refere to these guidelines for performing stability studies.

## 4.10. Prescribing information for veterinarian (Clinical & Toxicological Data):

The information shall be submitted in Arabic and English languages and shall include the following:

- Product name.
- Composition: The active ingredient/s and its quantity per unit dose.
- Therapeutic class.
- Product description.
- Pharmacokinetics.
- Indications.
- Contraindications.
- Warning including data on teratogenecity, use in pregnancy, use in lactating animals or layers, use in animals with impaired organ function (kidney, liver …..etc).
- Adverse affects/undesirable effects.
- Precautions including drug and diagnostic interactions.

- Dose and administration.
- Overdose- manifestations and treatment.
- Withdrawal period(s) (where applicable).
- References from where the information were collected.
- Package
- Storage.

**4.11. Packaging and labeling (Include the primary and secondary packaging material).**

- Specifications of the packaging material in immediate contact with the medicinal product (including the design layout, composition of packaging material, safety of the pack from the standard point of sealing and child -proofing measures and quality testing including a certificate of analysis).
- Packaging material specifications, must include the following information:
  - A code reference for every packaging material.
  - The nature of the material, dimensions, composition (where applicable), and illustrative drawing.
  - All the required tests to show conformity with the specifications for the primary packaging material the pharmacopoeial tests are required.
  - Approved supplier(s).
  - Sampling instructions.
  - The procedure of taking packaging samples for analysis.
- The label ( both the inner and outer) of the packaging material should contain the following information:
  - Brand name of the product in Arabic and English.
  - International non-proprietary name (INN).
  - Pharmaceutical dosage form.
  - Route of administration.
  - Name and address of the manufacturer in Arabic and English.

- Name and address of the importer in Arabic and English (For imported drugs).
- The logo of the manufacturer.
- The active ingredient and their quantities per unit dose of the product, in their generic name,
- Quantities of drug (in gm, ml, lit… etc).
- Batch number.
- Expiry date.
- Storage condition.
- Any other instruction pertinent to the use of the product (e.g. for external use, shake well before use for veterinary use, prescription only medicine…etc).
- Dosage and administration.
- Withdrawal periods.

- Due to lack of space, the warnings, precautions, address of the manufacturer, withdrawal period, and storage conditions may be omitted on the primary container if it is a blister or strip pack, or a vial less than 10ml.

## 6. Renewal of registration:

1. Application for renewal of registration shall be submitted to the Drug Control and Registration, every five years, not later than four months prior to the expiry of the registration. In extenuating circumstances the application will be accepted at a later date but not later than two months prior to the expiry of the registration.

2. The application shall include the following:
   - Application form for the renewal of registration in three copies signed by the responsible pharmacist/vet..
   - Original receipt confirming payment of fees for the renewal of registration.
   - The latest method(s) of analysis for the finished product.
   - The finished product specifications.
   - The latest master formula for the product.
   - The latest stability study of the product (shelf life).

3. Sufficient samples for analysis accompanied by a reference standard material from the active(s) constituent.

4. Samples from the latest secondary packaging materials and from the aluminium foil primary packaging material.

5. The Department of Drug Control and Registration reserves the right to ask for any additional documents with regard to the registered drug file.

## 7. Amendment to the registration of a veterinary product:

Amendments to the registration of a veterinary medicinal product shall be applied. Manufacturer who wishes to make any amendment to the registration of a product shall apply for to Drug Control and Registration Department.

Changes or variations requirements are illustrated in ***Appendix (1).*** Any other changes not included in the appendix of changes shall be applied for and the department shall notify the applicant with the requirements and decision.

1. Application form should be submitted to the Drug Control and Registration Department in three copies.
2. The application shall be submitted together with an explanation regarding the nature of the change, including relevant background material (e.g. stability data).
3. A change in indications must include the relevant pharmacological and clinical data relevant to the requested indication.
4. An application for a change in the site of manufacture shall be accompanied by:
   - Declaration by the manufacturer that there has been no change in the manufacturing procedure or in the drug specification.
   - Certificate of good manufacturing practice.
   - Certificate of analysis from the manufacturer.
   - The plant master file for the new site.
5. For imported medicinal products, a document confirming that the requested amendment has been approved in the country of manufacturer, shall be attached.
6. The Department of Drug Control & Registration reserve the right to require additional data or waive any of the above requirements.

## 8. Application Forms

1. Pre-approval application for veterinary medicinal product registration
2. Application form for veterinary medicinal product registration
3. Registration renewal application form
4. Application form for a quality control certificate
5. Amendment application form

# Pre-approval Application for Registartion of Veterinary Medicinal Product

To: The Director of Drug Control and Registration Department

*I hereby request your approval to register the following veterinary medicinal product:-*

1. **Applicant:**
   - Name of the applicant (responsible pharmacist/vet.):
     ……
     ……
     ……
   - Address:
     ……
     ……
     ……

2. **Veterinary Medicinal product:**
   Name of product : …….
   Suggested: …….
   Dosage form: ……
   Packaging: ……
   Strength: ……

3. **Manufacturer:**
   Name: ……..
   Address: ……..
   Address of the branch supplying Palestine (for imported drugs only):
   ……
   ……

4. **Purpose of registration:**
   ( ) Manufacturing and marketing ( ) Importing and marketing
   ( ) Packing and marketing
   ( ) Veterinary use

5. **Suggested indications of the drug:**
   ……
   ……

6. **Similar international brand name(s) containing the same active ingredient/s and their manufacturers:**
   ……
   ……
   ……

**7. Price:**

Suggested price to consumer: ……..
Export price to Palestine ( F.O.B/ C&F):…….
Price to the public in the country of origin: …….

**Signature of the Responsible Pharmacist** **Date**

**……** **……**

**********

***For the office use only***

Date of receiving the application: …….…….
Name of person receiving the application: ……..…….

Decision:
( ) Approved
( ) Rejected for:
……
……..

( ) Others:
……
……
…….

**……** **……**

**Head of Reg. Division** **Director of DDCR**

# Application Form for Veterinary Medicinal Product Registration

To: The Director of Drug Control and Registration Department

**For official use only**
Application No.:……..…
Date received: ……...
Name of Receiver: ……..…...

## 1. Particulars of applicant:

Name of the Applicant: .....

Address: …….

Telephone No. ..... Telefax No.....

Email:..... Website.....

## 2. Particulars of the manufacturer(s) and activity:

| Name: | Physical address of Production site | Activity |
|---|---|---|
| 1. ..... | | |
| 2. ..... | | |
| 3..... | | |

(Attach copies of GMP certificate from the country of origin drug regulatory Authority Local (DRA) for each site)

## 3. Particulars of the product:

Name of the product: .....
Dosage form: ……..……..…….
Strength: ……..…….
Description of the product (colour, shape, size, etc):
……..……
……..…….
Commercial presentation (packaging and pack sizes applied for in which stability studies were conducted):
……..…….
Route of administration:……..
Distribution category requested (POM/OTC):……....
Proposed shelf life in months:…….
Storage conditions:……..

## 4. Purpose of registration:

( ) Manufacturing & Marketing ( ) Importing & Marketing ( ) Packaging & Marketing
( ) Veterinary use .

## 5. Price :

Suggested price to the consumer: .....
Export price to Palestine (F.O.B/C&F): .....
Price to the public in the country of origin: .....

## 6. Composition:

6.1 Active constituents
Name and quantities:
.....
.....
.....
.....

6.2 Other constituents (Name only):
.....
.....
.....
(Note : For empty shell capsules indicate the type and colour No.)

6.3 Overage:
……
……
(Note: If an overage is included it should be stated in what percentage and for what reason).

6.4 Source of active ingredients:
Name: .....
Address: .....

## 7. Indicate type and percentage of:

7.1 Colouring matter:
.....
.....
.....

7.2 Preservative:
.....
.....
.....

## 8. Quality control:

Raw material (active) specifications including manufacturing processes and analytical control procedures carried out as release requirements (to be attached):
.....
.....
.....

In-process controls performed (to be attached):

.....
.....

Final product specifications and analytical control procedures carried aout as release requirements (to be attached):

.....
.....

## 9. Specifications of packaging material:

Primary container(s):

.....
.....

Secondary container(s):

.....
.....

## 10. Stability and shelf life:

10.1 Type of study conducted:

( ) Accelerated ( ) Shelf life ( ) Long Term

10.2 Anticipated shelf life of the product according to the stability study:

.....
.....

10.3 Change in the physical characteristics anticipated during storage:

.....
.....
.....

10.4 Chemical changes anticipated during storage:

.....
.....
.....

## 11. Label and insert information:

11.1 Directions for use:

.....
.....
.....

11.2 Contraindication and side effects:

.....
.....

11.3 Warning:

.....
.....
.....

11.4 Storage conditions:

.....
.....
.....

11.5 Withdrawal periods:

.....
.....
.....

11.6 Details of drug residues in species intended for human consumption:

.....
.....
.....

## 12. Clinical use:

12.1 Pharmacological action and recommended clinical use :

.....
.....
.....
.....

12.2 Proposed route(s) of administration:

.....
.....
.....

12.3 Recommended dosage:

.....
.....
.....

## 13. Mechanism of Action: -

.....
.....
.....
.....
.....
.....
.....
.....
.....
.....

## 14. Toxicology (Pathology, toxicology, teratology): -

.....
.....
.....
.....
.....
.....
.....
.....
.....

## 15. Current registration status: -

State the names of all countries (including the country of manufacture) where the product is registered (for imported products):

.....
.....

## 16. Certificate of a pharmaceutical product (WHO type) (for imported products): -

.....
.....

## 17. Supporting materials: -

17.1 Samples:

- Provide a minimum quantity of the product in commercial pack sufficient to conduct three sets of full analysis.
- Provide a minimum of 200mg of reference standards working standard with the corresponding certificate of analysis.

17.2 Product information:

- Provide copies of package inserts, labels and samples of packaging materials.
- Provide samples of the proposed advertising and promotional materials if any.

## 18. Declaration: -

I, the undersigned hereby apply for registration of the product detailed above and declare that all the information contained herein and in the annextures is correct and true.

I enclose a fee of US $: ……. Receipt.
No……...
Date:……...
Signed:……
Full name of signatory:…….
Official designation and qualification:……..

**********

***For the use of Drug Technical Committee***

## 19. Approval of registration :

19.1 Marketing restriction: ( ) Prescription only medicine ( ) For veterinary use only
( ) Other restrictions:.....

19.2 Indication ( ) The requested indication will be approved.
( )The indication will be as follow:
.....
.....

19.3 Warning that shall appear on the label/ package
( ) Other warning or statement/s may be required for this product: .....
.....
.....

19.4 Shelf life: ……..

19.5 Registration number: .....

19.6 Registration valid from ..... To .....

19.7 The decision of the Drug technical Committee:
( ) Approved ( ) Rejected: ……
( ) Others:……

**Signature of the members of the Drug technical committee:**

**Chairman:……..**

**Member:……, Member:……,**

**Member:……, Member:……,**

**Member:……, Member:……,**

**Member:……, Member:……,**

**Member:……, Member:……,**

# Check List for Submission of Data

**Name of the Product: ……..……..…**

**Name of Manufacturer: ……..……..**

**Name of Importing Company: ……...……...**

( ) Application forms for registration.
( ) Original receipt confirming payment of the fees.
( ) GMP Certificate.
( ) Agency/ Distribution agreement.
( ) Free sale certificate.
( ) Certificate of pharmaceutical ptroduct (CPP WHO type)
( ) package insert.
( ) Master formulation.
( ) Production procedures.
( ) Raw materials monographs.
( ) Drug Master File for active material for non-pharmacopoeia material)
( ) Pharmacotechnical data.
( ) In-process controls.
( ) Methods of analysis.
( ) Validation of analytical methods.
( ) Packaging materials specifications.
( ) Secondary packaging material draft artwork (coloured).
( ) Stability study report data and proposed shelf-life & chromatograms.
( ) Degradative materials and test.
( ) Prescribing information for the vet. & references (package insert).
( ) Sample of the medicinal product in its proposed packaging including label.
( ) Original certificate of analysis for finished product from manufacturer.
( ) Reference standards and original certificate of analysis.
( ) Summary of clinical, toxicological and withdrawal period

Signature …….. Date……..

# Registration Renewal Application Form

To: The Director of Drug Control and Registration Department
*We hereby request that the registration of the following veterinary medicinal product to be renewed.*

- **Applicant information**:
  - Applicant's Name (Responsible pharmacist or responsible vet)……
  - Manufacturer name and address:……..
  - Name and address of the importer (for imported drugs only): ……..…
- **Product information**:
  - Registration No:……
  - Name of the medicinal product: …….
  - Dosage form and strength: ……..
  - Quantity per pack: ……..
  - Purpose of re-registration:
  - ( ) Manufacturing and marketing.
  - ( ) Import and marketing.
  - Any previousely approved restrictions on the marketing of the product:
    ……
    ……

**Signature of the responsible pharmacist/Vet.** **Date**

**……** **……**

**********

Attachments:

☐ Original receipt confirming payment of re-registration fees.

☐ Latest master formula.

☐ Latest method(s) of analysis for the finished.

☐ The shelf-life stability study.

☐ The latest packaging materials specifications (primary and secondary) attached with sample from secondary packaging materials or coloured artwork.

☐ Valid certificate of pharmaceutical product (CPP) (Imported drugs).

☐ Sufficient samples from finished products and reference materials for analysis purposes.

**********

***For Office use only:***

- Name of receiver:……..
- Date receiving:……
- Remarks:……

Signature: …… Date:……

# Application Form for Quality Control Certificate

To: The Director of Drug Control and Registration Department

We hereby request that the following veterinary medicinal product be tested for quality and that a quality certificate be issued accordingly:

- Name of the medicinal product:…… ……..…
- Dosage form: ……...…
- Composition: ……..……..……
- Strength: ……..……
- Batch No.: …… Expiry date……...…
- Name of the manufacturer:……..……
- Name of the agent (for Imported drugs):……

**********

## Attachments:

☐ Sufficient samples.

☐ Method(s) of analysis.

☐ Finished product specifications.

☐ Reference standard

☐ Certificate of analysis from manufacturer

☐ Others……..

**Name & Signature of the responsible pharmacist** **Date**

**……** **……**

**********

For office use only

- Date of receiving the application: ……
- Name of receiver:……..……..
- Result:
  ( ) Pass ( ) Fail ( )Others
  Remarks:……

# Amendments Application Form

To: The Director of Drug Control and Registration Department

*We hereby request the approval of the changes/variations on the registered veterinary product mentioned bellow*

## Details of the current registration:

- Name of the veterinary medicinal medicinal product:…….…….....
- Registration number: ……..…..
- Dosage form:……..……..….
- Composition and strength:……...….
- Manufacturer address: …….…….…..…..…
- Manufacturing site and address (if different from above)……..
- Importing agent and address:……...……..…

## Details of the requested amendment:

- Tabulate the requested amendment(s) in away to show the current and new suggested change(s) *(use additional pages of necessary).*
  ……
  ……
  ……
- Reason(s) for the amendment accompanied with relevant supporting data.
  ……
  ……
  ……
- Letter of approval of the amendments from the drug regulatory authority in the country of original.
  ……
  ……
  ……

## Declaration of the applicant:

*I hereby declare that:*

☐ The change(s) will not adversely affect the quality, efficacy and safety of the product.

☐ All condition as set for the notification(s) concerned are fulfilled.

☐ The required documentation as specified for the notification(s) have been submitted.

| Applicant`s Name | Applicant`s Signature | Date |
|---|---|---|
| …….. | …… | …… |

**********

***For Office Use Only:***

- Date of receiving of the application:…….…….
- Name of the receiver:…….……
- Amendment decision:

□ The requested amendment(s) is approved.

□ The requested amendment(s) is rejected for the following reasons:

1. …….
2 ……...……...
3. ……..…….

□ Others, the applicant is requested to:

……
……
……

**……..…..** **……**

**Head of registration division** **Director of DDCR**

## 9. Appendixes

1. **Appendix (1):** File Requirements for Variations (Amendments)
2. **Appendix (2):** Guide to transfer of product marketing authorisations
3. **Appendix (3):** Requirements for Registration of Pharmaceutical Manufacturing Site

# Appendix (1)

# File Requirements for Variations (Amendments)

| | | |
|---|---|---|
| 1. | **Change or inclusion of manufacturer of active pharmaceutical ingredient (API)** | |
| | *Documentation to be submitted* | |
| | 1) | Pharmacopoeia Certificate of Suitability (CEP) for the (API) or Drug Master File; |
| | 2) | Tabulation of the differences compared with the registered manufacture information (if applicable); |
| | 3) | Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the drug substance from the current and proposed manufacturers/sites; |
| | 4) | Stability study for the finished product manufactured with the drug substance from the prosed manufacturer in accordance with the relevant stability guidelines. |
| 2. | **Change or inclusion of manufacturing site(s) for part or all of the manufacturing process of the drug product, with:**<br>**2.1. No change in the manufacturing process and in the release and shelf life specifications, including test methods**<br>**2.1. With changes in the manufacturing process and/or test methods** | |
| Condition | | |
| | - | Not applicable to changes relating to manufacturer responsible for batch release or a site where only batch release takes place. |
| | *Documentation to be submitted* | |
| | **2.1 No change in the manufacturing process and in the release and shelf life specifications, including test methods** | |
| | 1) | Proof that the proposed site is appropriately authorised for the pharmaceutical form concerned: a GMP certificate; |
| | 2) | Official letter authorising the proposed site to manufacture the product; |
| | 3) | Product formula; |
| | 4) | Specification of drug substance; |
| | 5) | Release and shelf life specifications of drug product; |
| | 6) | Relevant stability data of at least 6 months on 2 batches (pilot/production) in accordance with the relevant guidelines with undertaking to conduct on-going stability study and report if any results fall outside shelf life specification (with proposed action); |
| | 7) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 8) | Batch analysis data on a minimum of one production batch and two pilot batches (or two production batches) simulating the production process and comparative data on the last 3 batches from the previous site; batch data on the next 2 full production batches should be available upon request or reported if outside release and shelf life specifications (with proposed action); |
| | 9) | For sterile or parenteral products, validation data of the manufacturing process and sterilization process at the proposed site for products should be provided. |
| | 10) | Official letter declaring that the formulation, drug substance source & specification, manufacturing process, analytical test methods, release and shelf life specifications have not changed; |
| | **2.2 With changes in the manufacturing process and/or test methods** | |
| | 11) | In addition to **2.1** documentation 1 to 10; |
| | 12) | Comparative dissolution profile data of at least one representative pilot/production batch of the drug product in the proposed and current sites for solid dosage forms. |
| | 13) | Justification for not submitting a new bioequivalence study. |

| | | |
|---|---|---|
| | 14) | Official letter declaring that the formulation, drug substance source & specification, release and shelf life specifications, and/or manufacturing process and/or analytical test methods have not changed (where applicable); |
| | 15) | Tabulation of the changes and differences; |
| | 16) | Validation data on manufacturing process and/or analytical method (where applicable). |
| 3. | **Change or inclusion of primary packager** | |
| | *Conditions* | |
| | - | No change in the manufacturer, manufacturing process, release and shelf life specifications, including test methods, and packaging materials; |
| | - | The change does not relate to sterile products. |
| | *Documentation to be submitted* | |
| | 1) | Proof that the proposed site is appropriately authorised for the packaging activity concerned: GMP certificate; |
| | 2) | Official letter authorising the proposed site to package the product and stating the types of activity performed by the packager; |
| | 3) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 4) | A declaration from the applicant that the relevant stability studies in accordance with the relevant guidelines have been started (on at least two pilot scale or production scale batches) and that the relevant stability studies will be finalised; data should be provided only if outside shelf life specification (with proposed action) or when requested. |
| 4. | **Change of shelf life of the drug product** | |
| | *Condition* | |
| | - | The studies must show conformance to the current shelf life specification. |
| | *Documentation to be submitted* | |
| | 1) | Results of appropriate real time stability studies of at least two production scale batches of the product in the authorised packaging material covering the duration of the requested shelf life in accordance with the relevant stability guidelines; |
| | 2) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). |
| 5. | **Change of shelf life after first opening** | |
| | *Condition* | |
| | - | Studies must show conformance to the current shelf life specification. |
| | *Documentation to be submitted* | |
| | 1) | Results of appropriate real time stability studies of at least two production scale batches of the product in the authorised packaging material after first opening in accordance with the relevant stability guidelines; results of appropriate microbiological testing should be included (where applicable); |
| | 2) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). |
| 6. | **Change of shelf life after reconstitution** | |
| | *Condition* | |
| | - | Studies must show conformance to the current shelf life specification for the reconstituted product. |
| | *Documentation to be submitted* | |
| | 1) | Results of appropriate real time stability studies of at least two production scale batches of the reconstituted product in accordance with the relevant stability guidelines; results of appropriate microbiological testing should be included (where applicable); |
| | 2) | Revised drafts of the package insert and labelling (incorporating the proposed variation (where applicable). |
| 7. | **Change of storage conditions** | |
| | *Condition* | |

| | | |
|---|---|---|
| | - | The studies must show conformity to the current shelf life specification. |
| | *Documentation to be submitted* | |
| | 1) | Results of appropriate real time stability studies of at least two production scale batches of the product up till the approved shelf life and in the authorised packaging material. |
| | 2) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). |
| 8. | **Change of pack size (volume) or inclusion of new pack size for a sterile drug product** | |
| | *Conditions* | |
| | - | Release and shelf life specifications of the drug product are not affected; |
| | - | The proposed pack size is consistent with the dosage regimen and duration of use as approved in the package insert; |
| | - | The packaging material remains the same. |
| | *Documentation to be submitted* | |
| | 1) | Justification that the proposed pack size is consistent with the dosage regimen and duration of use as is approved in the package insert; |
| | 2) | Validation data of the manufacturing process, sterilization and container closure system (where applicable); |
| | 3) | Results of the stability study for at least 6 months (2 production scale) of the proposed pack size with undertaking to continue the stability studies up till the proposed shelf life and to report if any results fall outside shelf life specification; |
| | 4) | Revised drafts of the package insert and labelling incorporating the proposed variation; |
| | 5) | A declaration from the applicant that the release and shelf life specifications of the drug product are not affected. |
| 9. | **Change of primary packaging material** | |
| | *Conditions* | |
| | - | Release and shelf life specifications of the drug product are not affected. |
| | *Documentation to be submitted* | |
| | 1) | Validation data of the manufacturing process, sterilization and container closure system (where applicable); |
| | 2) | Results of the stability study for at least 6 months (2 production scale) of the proposed primary packaging material with undertaking to continue the stability studies up till the proposed shelf life and report if any results fall outside shelf life specification (with proposed action) or when requested; |
| | 3) | A declaration from the applicant that the release and shelf life specifications of the drug product are not affected. |
| 10 | **Change of product labelling** | |
| | *Conditions* | |
| | - | Product labelling refers to package insert, patient information leaflet, unit carton label, inner label and/or blister strips; |
| | - | The change is not a major variation (MAV); |
| | *Documentation to be submitted* | |
| | 1) | Current approved product labelling |
| | 2) | Proposed product labeling. |
| | 3) | Justifications for the changes proposed. |
| | 4) | Approval from a reference regulatory agency containing the proposed changes (where applicable). |
| 11 | **Change of contact person in company** | |
| | *Condition* | |
| | - | The product licence holder remains the same. |
| | *Documentation to be submitted* | |
| | 1) | Particulars of the contact person. |

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| 12 | **Change of product name** | |
| | *Conditions* | |
| | - | There is no change to the product (formulation, release and shelf life specifications, manufacturing source and process) except the product name change; |
| | - | No confusion with another medicinal product either when spoken or written; |
| | - | The new name does not (1) suggest greater safety or efficacy than supported by clinical data (2) imply a therapeutic use (3) imply superiority over another similar product (4) imply the presence of substance(s) not present in the product. |
| | *Documentation to be submitted* | |
| | 1) | Official letter authorising the change of product name (for imported drugs) |
| | 2) | A declaration from the applicant that there is no change to the product except name; |
| | 3) | Official letter of commitment to inform users of the relevant changes, and that the current product stocks will be exhausted before the product labelled with the new name is marketed; |
| | 4) | Revised draft package insert and labelling incorporating the proposed variation; |
| | 5) | CPP with the new name (where applicable). |
| 13 | **Change of batch numbering system** | |
| | *Documentation to be submitted* | |
| | 1) | Description of batch number system; |
| | 2) | Official letter stating the commencement date of the change. |
| 14 | **Change of the name or address (e.g. postal code, street name) of a manufacturer of the active ingredient (API).** | |
| | *Condition* | |
| | - | The manufacturing site of the drug substance remains the same |
| | *Documentation to be submitted* | |
| | 1) | Updated information of the manufacturer of the drug substance; |
| | 2) | A declaration from the applicant that manufacturing site remains the same. |
| 15 | **Change of the name or address (e.g. postal code, street name) of a manufacturer of drug product** | |
| | *Condition* | |
| | - | The manufacturing site remains the same. |
| | *Documentation to be submitted* | |
| | 1) | Official letter authorising the manufacturer with new name/address to manufacture the drug product; |
| | 2) | GMP certificate with new name or address; |
| | 3) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 4) | A declaration from the applicant that the change does not involve a change of manufacturing site, manufacturing process and quality of product; |
| | 5) | Official letter stating the commencement date of the change. |
| 16 | **Deletion of pack size for a drug product** | |
| | *Condition* | |
| | - | An alternative pack size is registered. |
| | *Documentation to be submitted* | |
| | 1) | Reason for deletion; |
| | 2) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). |
| 17 | **Change of manufacturing process of the active ingredient.** | |
| | *Conditions* | |

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| | - | The synthetic route remains the same; |
| | - | Specification of the (API) is not adversely affected; |
| | - | No change in the physical properties; |
| | - | No new impurities or change in level of impurities which would require further qualifications in safety studies. |
| | *Documentation to be submitted* | |
| | 1) | Tabulation of the current and new process with changes highlighted; |
| | 2) | Batch analysis of the drug substances |
| | 3) | Batch analysis data (in a comparative tabulation form) of at least two batches (pilot scale or production scale) manufactured according to the currently approved and proposed process. |
| | 4) | Appropriate evidence must be provided if any potential new impurities are detectable at an acceptable limit of detection; |
| | 5) | A declaration from the applicant that no new impurities have been introduced at or above the accepted threshold for qualification of impurities or that there is no increase in the level of impurities, which require further safety studies; |
| | 6) | A declaration from the applicant that the specification of the drug substance has not changed or if there is any change to the specification (i.e. tightening), the texts of the current and proposed specifications should be provided (in a comparative tabulation form where possible); |
| | 7) | A declaration from the applicant that the relevant stability studies of the drug substance in accordance with the relevant guidelines have been started and that the relevant stability studies will be finalised; data should be provided only if outside specification (with proposed action). |
| 18 | **Change of the specification of a drug.**<br>**18.1 Specification limits are tightened**<br>**18.2 Addition of new test parameter and limits** | |
| | *Condition* | |
| | - | New test method does not concern a novel non-standard technique or a standard technique used in a novel way. |
| | *Documentation to be submitted* | |
| | **18.1 Specification limits are tightened** | |
| | 1) | Tabulation of the current and revised specification of drug substance with changes highlighted; |
| | 2) | Revised specification of drug substance; |
| | 3) | Batch analysis of the drug substance for all tests in the new specification. |
| | **18.2 Addition of new test parameter and limits** | |
| | 4) | In addition to 12.1 Documentation 1 to 3; |
| | 5) | Description of any new analytical method and summary of the validation data. |
| 19 | **Change of test procedure of drug substance** | |
| | *Condition* | |
| | - | Results of method validation show new test procedure to be at least equivalent to the former procedure. |
| | *Documentation to be submitted* | |
| | 1) | Description of the analytical methodology, a summary of validation data, and comparative analytical results between the current test and the proposed one, if appropriate; |
| | 2) | Specification of the drug substance; |
| | 3) | A declaration from the applicant that the specification of the drug substance has not changed. |
| 20 | **Change to comply with Pharmacopoeias for drug substance** | |
| | *Conditions* | |
| | - | Change is made exclusively to comply with an update of the relevant monograph of the |

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| | | Pharmacopoeia; |
| | - | Exclude the change from one pharmacopoeia to another. |
| | *Documentation to be submitted* | |
| | 1) | Tabulation of the current and revised specifications with changes highlighted; |
| | 2) | Revised specification of the drug substance; |
| | 3) | Batch analysis of the drug substance for all tests in the new specification. |
| 21 | **Extension of the shelf life or retest period of the drug substance** | |
| | *Condition* | |
| | - | The studies must show compliance with specification |
| | *Documentation to be submitted* | |
| | 1) | Stability data of the drug substance should be presented on at least two pilot or production scale batches of the requested shelf life or retest period; |
| | 2) | Specification of the drug substance. |
| 22 | **Change of imprints, bossing or other markings (except scoring/breaking line) on tablets or printing on capsules including addition or change of inks used for product marking** | |
| | *Conditions* | |
| | - | New markings do not cause confusion with other tablets or capsules; |
| | - | The are approved for pharmaceutical use; |
| | - | Release and shelf life specifications of the drug product have not changed (except for appearance). |
| | *Documentation to be submitted* | |
| | 1) | Details of the proposed new inks (where applicable); |
| | 2) | Detailed drawing or written description of the current and proposed imprint/bossing/markings/ink; |
| | 3) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 4) | Official letter of commitment to inform users of the relevant changes, and that the current product stocks will be exhausted before the product labelled with the new name is marketed; |
| | 5) | A declaration from the applicant that the release and shelf life specifications of the product have not changed (except for appearance). |
| 23 | **Change of dimensions of tablets, capsules, suppositories or pessaries without change in qualitative and quantitative composition and mean mass**<br>**23.1 Conventional dosage form, suppositories and pessaries**<br>**23.2 Critical dosage form and scored tablets** | |
| | *Conditions* | |
| | - | No change in dissolution profile; |
| | - | Release and shelf life specifications of the drug product have not changed (except for dimensions). |
| | *Documentation to be submitted* | |
| | **23.1 Conventional dosage form, suppositories and pessaries** | |
| | 1) | Detailed drawing or written description of the current and proposed appearance; |
| | 2) | Release and shelf life specifications of the drug product; |
| | 3) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). |
| | **23.2 Critical dosage form and scored tablets** | |
| | 4) | In addition to 17.1 documentation 1 to 3; |
| | 5) | Comparative dissolution data on at least one pilot/production batch of the current and proposed dimensions. |
| | 6) | Where applicable, data on the test for uniformity of content of the subdivided parts of tablets at release should be submitted and commitment to conduct the test at the end of |

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| | | shelf life, data should be provided only if outside the release and shelf life specifications (with proposed action). |
| 24 | **Replacement of an excipient with a comparable excipient** | |
| | *Conditions* | |
| | - | Same functional characteristics of the excipient; |
| | - | No change in dissolution profile for solid dosage forms; |
| | - | The release and shelf life specifications of the drug product have not changed (or have tightened), except for the replacement of the excipients. |
| | *Documentation to be submitted* | |
| | 1) | Justification for the change/choice of excipients must be given by appropriate development pharmaceutics (including stability aspect and antimicrobial preservation where appropriate); |
| | 2) | Tabulation of the current and revised product formulation with changes highlighted; |
| | 3) | Revised product formulation; |
| | 4) | Release and shelf life specifications and batch analysis of the drug product; |
| | 5) | Specifications of new excipient; |
| | 6) | Comparative dissolution profile data of at least one representative pilot/production batch of the drug product in the new and old composition for solid dosage forms. |
| | 7) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 8) | A declaration from the applicant that the new excipient does not interfere with the drug product release and shelf life specifications test method; |
| | 9) | A declaration from the applicant that the release and shelf life specifications of the drug product have not changed; |
| | 10) | A declaration from the applicant that the relevant stability studies have been started (on at least two pilot scale or industrial scale batches) and that the relevant stability studies will be finalised; data should be provided only if outside the shelf life specification (with proposed action) or when requested. |
| 25 | **Quantitative change of an excipient** | |
| | *Conditions* | |
| | - | Total quantitative change within ± 5%; |
| | - | Disintegrant: Starch (±3), other (±1%); |
| | - | Binder (±0.5%); |
| | - | Lubricant: Ca or Mg Strearate (±0.25%), other (±1%); |
| | - | Glidant: Talc (±1%), other (±0.1%); |
| | - | Film Coat (±1%); |
| | - | No change in the dissolution profile for solid dosage forms; |
| | - | Release and shelf life specifications of the drug product have not changed. |
| | *Documentation to be submitted* | |
| | 1) | Justification for the change must be given (including stability aspect, and antimicrobial preservation where appropriate); |
| | 2) | Comparative dissolution profile data of at least one representative pilot/production batch of the drug product in the new and old composition for solid dosage forms. |
| | 3) | Justification for not submitting a new bioequivalence study according to the current Bioavailability and Bioequivalence guidance; |
| | 4) | Tabulation of the current and revised product formulation with changes highlighted; |
| | 5) | Revised product formulation; |
| | 6) | Release and shelf life specifications and batch analysis of drug product; |
| | 7) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 8) | A declaration from the applicant that the change of excipients does not interfere with the |

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| | | drug product release and shelf life specifications test method; |
| | 9) | A declaration from the applicant that the release and shelf life specifications of the drug product have not changed; |
| | 10) | A declaration from the applicant that the relevant stability studies have been started (on at least two pilot scale or industrial scale batches) and that the relevant stability studies will be finalised; data should be provided only if outside the shelf life specification (with proposed action) or when requested. |
| 26 | **Change of the colouring system of the product (addition, deletion or replacement of colourant(s)** | |
| | *Conditions* | |
| | - | Same functional characteristics. |
| | - | The colouring system must be for pharmaceutical use; |
| | - | The release and shelf life specifications of the drug product have not changed, except for the change in appearance/colour. |
| | *Documentation to be submitted* | |
| | 1) | Qualitative and quantitative information of the colouring agent; |
| | 2) | Revised product formulation; |
| | 3) | Release and shelf life specifications of the drug product; |
| | 4) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 5) | Official letter of commitment to inform users of the relevant changes, and that the current product stocks will be exhausted before the product with the proposed variation is marketed; |
| | 6) | A declaration from the applicant that the change in the colouring system does not interfere with the drug product release and shelf life specifications test methods; |
| | 7) | A declaration from the applicant that the release and shelf life specifications have not changed (except for appearance); |
| | 8) | A declaration from the applicant that the relevant stability studies have been started (on at least two pilot scale or industrial scale batches) and that the relevant stability studies will be finalised; data should be provided only if outside the shelf life specification (with proposed action) or when requested |
| 27 | **Change of the flavouring system of the product (addition, deletion or replacement of flavour(s)** | |
| | *Conditions* | |
| | - | Proposed flavour must be approved for pharmaceutical use; |
| | - | The release and shelf life specifications of the drug product have not changed, except for the change in flavour. |
| | *Documentation to be submitted* | |
| | 1) | Qualitative and quantitative information of the flavouring agent; |
| | 2) | Revised product formulation; |
| | 3) | Release and shelf life specifications of the drug product; |
| | 4) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 5) | Official letter of commitment to inform users of the relevant changes, and that the current product stocks will be exhausted before the product with the proposed variation is marketed; |
| | 6) | A declaration from the applicant that the change of flavour(s) does not interfere with the drug product release and shelf life specifications test method; |
| | 7) | A declaration from the applicant that the release and shelf life specifications of the product have not changed (except for flavour); |
| | 8) | A declaration from the applicant that the relevant stability studies have been started (on at least two pilot scale or industrial scale batches) and that the relevant stability studies will be finalised; data should be provided only if outside the shelf life specification (with |

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| | | proposed action) or when requested. |
| 28 | **Quantitative change in coating weight of tablets or weight of capsule shells** | |
| | *Conditions* | |
| | - | No change in dissolution profile; |
| | - | The product release and shelf life specifications have only been updated in respect of weight and dimensions, if applicable. |
| | *Documentation to be submitted* | |
| | 1) | Comparative dissolution profile data of at least one pilot/production batch of the drug product in the new and old composition, (for modified release products to provide in vitro data which has been correlated with in vivo data); |
| | 2) | Revised release and shelf life specifications of the drug product; |
| | 3) | A declaration from the applicant that the change does not interfere with the drug product specifications test method; |
| | 4) | A declaration from the applicant that the release and shelf life specifications of the drug product have not changed (except for average weight). |
| 29 | **Addition or replacement of a manufacturer for secondary packaging** | |
| | *Documentation to be submitted* | |
| | 1) | Proof that the proposed site is appropriately authorised for the packaging activity concerned: GMP certificate; |
| | 2) | Official letter authorising the new manufacturer to perform secondary packaging; |
| | 3) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). |
| 30 | **Addition or replacement of the company or manufacturer responsible for batch release** | |
| | *Condition* | |
| | - | Method transfer from the current to the new site has been successfully completed. |
| | *Documentation to be submitted* | |
| | 1) | Official letter authorising the company/manufacturer to be responsible for batch release; |
| | 2) | GMP certificate of the proposed site; |
| | 3) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable). |
| 31 | **Change of batch size of drug product** | |
| | *Condition* | |
| | - | The change does not affect consistency of production; |
| | - | The change relates only to standard immediate release oral dosage forms and to non-sterile liquid forms; |
| | - | Validation has been successfully carried out according to a written protocol with at least three batches from the proposed new batch size. |
| | *Documentation to be submitted* | |
| | 1) | Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed batch sizes. Batch data on the next 2 full production batches should be available on request or reported if outside the shelf life specification (with proposed action); |
| | 2) | Release and shelf life specifications of the drug product; |
| | 3) | Official letter of commitment to put the product manufactured according to the proposed batch size under stability studies in accordance with relevant stability guidelines. |
| 32 | **Change of in-process controls applied during the manufacture of the drug product** | |
| | *Condition* | |
| | - | In-process limits are tightened or addition of new tests. |
| | *Documentation to be submitted* | |
| | 1) | A description of the analytical methodology and summary of validation data must be provided for all new analytical methods (where applicable); |

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| | 2) | Tabulation of the in-process controls and the relevant changes; |
| | 3) | Batch analysis data of one production batch of the drug product for all tests in the proposed specification (if applicable). |
| 33 | **Minor change of the manufacturing process of the drug product** | |
| | *Condition* | |
| | - | Release and shelf life specifications of the drug product are not adversely affected; |
| | - | New process must lead to an identical or better product regarding all aspects of quality, safety and efficacy; |
| | - | No change in the dissolution profile. |
| | *Documentation to be submitted* | |
| | 1) | Tabulation of the present process and the new process with changes highlighted; |
| | 2) | Appropriate justification and validation of the change should be provided where appropriate, especially for sterilization process; |
| | 3) | For solid dosage forms, dissolution profile data of one representative production batch. |
| | 4) | Release and shelf life specifications of the drug product. If there is any change of the specifications (i.e. tightening), the texts of the current and proposed specifications should be provided (side by side comparison where possible); |
| | 5) | Batch analysis of the drug product; |
| | 6) | Batch analysis data (in a comparative tabulation form) of at least one batch manufactured according to the currently approved and proposed process. |
| | 7) | A declaration from the applicant that the relevant stability studies of the drug have been started and that the relevant stability studies will be finalised; data should be provided only if outside specification (with proposed action). |
| 34 | **Change to comply with Pharmacopoeia for excipient** | |
| | *Condition* | |
| | - | Change is made exclusively to comply with an update of the relevant monograph of the Pharmacopoeia; |
| | - | Excluding the change from one pharmacopoeia to another. |
| | *Documentation to be submitted* | |
| | 1) | Tabulation of the current and revised specifications with changes highlighted; |
| | 2) | Specification of the excipient; |
| | 3) | Batch analysis of the excipient for all tests in the new specification. |
| 35 | **Change of specifications of excipient**<br>**35.1 Specification limits are tightened**<br>**35.2 Addition of new test parameter and limits** | |
| | *Documentation to be submitted* | |
| | **35.1 Specification limits are tightened** | |
| | 1) | Tabulation of the current and revised specification of the excipient with changes highlighted; |
| | 2) | Revised specification of the excipient; |
| | 3) | Batch analysis of the excipient for all tests in the new specification. |
| | **35.2 Addition of new test parameter and limits** | |
| | 4) | In addition to **29.1** documentation 1 to 3; |
| | 5) | Description of any new analytical method and summary of the validation data. |
| 36 | **Change of a test procedure for an excipient, including replacement of an approved test procedure by a new test procedure** | |
| | *Condition* | |
| | - | Appropriate validation studies have been performed. |
| | - | Results of method validation show new test procedure to be at least equivalent to the former procedure; |

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| | *Documentation to be submitted* | |
| | 1) | Description of the analytical methodology, a summary of validation data; |
| | 2) | Revised specification for impurities (if applicable); |
| | 3) | Comparative validation results showing that the current test and the proposed one are equivalent. |
| 37 | **Change of release and shelf life specifications of the drug product**<br>**37.1 Specification limits are tightened**<br>**37.2 Addition of new test parameter and limits** | |
| | *Documentation to be submitted* | |
| | **37.1 Specification limits are tightened** | |
| | 1) | Tabulation of the current and revised release and shelf life specifications of the medicinal product with changes highlighted; |
| | 2) | Revised release and shelf life specifications of the drug product; |
| | 3) | Batch analysis of the drug product for all tests in the new specification. |
| | **37.2 Addition of new test parameter and limits** | |
| | 4) | In addition to 31.1 documentation 1 to 3; |
| | 5) | Details of any new analytical method and summary of validation data. |
| 38 | **Change of test procedure of the drug product** | |
| | *Condition* | |
| | - | Results of method validation show new test procedure to be at least equivalent to the former procedure. |
| | *Documentation to be submitted* | |
| | 1) | Description of the analytical methodology, appropriate validation data, and comparative analytical results between the current test and the proposed one; |
| | 2) | Release and shelf life specifications of the drug product; |
| | 3) | A declaration from the applicant that the release and shelf life specifications of the drug product have not changed or if there is any change to the specifications, the texts of current and proposed specifications should be provided; |
| 39 | **Change of qualitative and/or quantitative composition of immediate packaging material** | |
| | *Condition* | |
| | - | The proposed packaging material must be at least equivalent or better than the current approved material in respect of its relevant properties; |
| | - | The change only concerns the same packaging (for example blister to blister); |
| | - | The change does not relate to sterile products. |
| | *Documentation to be submitted* | |
| | 1) | Justification for the change in packaging material and appropriate scientific studies on the new packaging; |
| | 2) | For semisolid and liquid dosage forms, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack); |
| | 3) | Specifications of the immediate packaging material; |
| | 4) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 5) | A declaration from the applicant that the relevant stability studies have been started (on at least two pilot scale or industrial scale batches) and that the relevant stability studies will be finalised; data should be provided only if outside the shelf life specification (with proposed action) or when requested; |
| | 6) | A declaration from the applicant that the product will meet the release and shelf life specifications. |
| 40 | **Change of container shape** | |

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| | *Condition* | |
| | - | No change in the qualitative and quantitative composition of the container and stability of the product in the container; |
| | - | The change does not concern a fundamental component of the packaging material which affects the delivery or use of the product; |
| | - | The change does not relate to sterile preparations. |
| | *Documentation to be submitted* | |
| | 1) | Details/Description of the new container shape; |
| | 2) | A declaration from the applicant that the specifications of the container (except for shape) have not changed; |
| | 3) | A declaration from the applicant that the release and shelf life specifications of the drug product have not changed; |
| 41 | **Change of pack size for a drug product** | |
| | *Condition* | |
| | - | Does not apply to sterile preparations, unless the change only concerns the number of containers in the outer packaging; |
| | - | Release and shelf life specifications of the drug product are not affected; |
| | - | The new size is consistent with the dosage regimen and duration of use as approved. |
| | - | The packaging material remains the same. |
| | *Documentation to be submitted* | |
| | 1) | Justification that the new size is consistent with the dosage regimen and duration of use as is approved. |
| | 2) | Revised drafts of the package insert and labelling incorporating the proposed variation (where applicable); |
| | 3) | A declaration from the applicant that the release and shelf life specifications of the drug product are not affected, the container and closure composition is unchanged; |
| 42 | **Addition or replacement of measuring device for oral liquid dosage forms and other dosage forms** | |
| | *Condition* | |
| | - | The size and where applicable, the accuracy of the proposed measuring device must be compatible with the approved posology; |
| | - | The new device is compatible with the medicinal product. |
| | *Documentation to be submitted* | |
| | 1) | Description of the device (including a drawing), where appropriate; |
| | 2) | The composition of the device material. Where applicable the materials should comply with the Pharmacopoeia; |
| | 3) | Justification that size and accuracy of the device are adequate for the posology as is approved in the product labelling; |
| | 4) | Revised draft of the package insert and labelling incorporating the proposed variation (where applicable). |
| 43 | Change of product labelling relating to:<br>• **Addition/deletion of bar code**<br>• **Replacement of distributor details**<br>• **Layout without altering text or meaning**<br>• **Deletion of indication**<br>• **Addition/deletion/replacement of pictures or diagrams that do not imply an unapproved indication** | |
| | *Condition* | |
| | - | No change to the text or meaning of the wordings; |
| | - | The change does not contain promotional information. |
| | *Documentation to be submitted* | |

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| | 1) | Current approved product labelling; |
| | 2) | Proposed product labeling. |
| | 3) | A declaration from the applicant that no other changes have been made to the labelling. |
| 44 | **Safety-related changes to product labelling** | |
| | *Condition* | |
| | - | Reduce the range of the product's target-patient population, or |
| | - | Add warnings, precautions, contraindications or adverse events/effects to the approved product labelling. |
| | *Documentation to be submitted* | |
| | 1) | Official letter outlining: (a) the reasons for the notification, (b) the status of the proposed changes in other countries; |
| | 2) | Current approved product labelling; |
| | 3) | Proposed product labeling. |
| | 4) | A declaration from the applicant that no other changes have been made to the labelling and that the changes are supported by data in the applicant's possession |

## Appendix (2)

# Guide to transfer of product marketing authorisations

1. **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.

**2. 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 ammendments 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 DDCR 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.

**3. MAKING AN APPLICATION**

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

- A copy of the legalised agreement concluded between the current MAH, the proposed new holder and the product owner to the mutual transfer of the product marketing authorisation.
- Signed statements 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: examples of the statements are attached

# Transfer Form
# Statement to be signed by the existing product marketing authorisation (registration) holder

**Reason for transfer application:**

1. I hereby notify the Department of Drug Control and Registration Ministry of Health Palestine, that

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

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

This file includes all the data in support of the original application together with all correspondence with the DDCR 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
# Statement to be signed by the proposed new product marketing authorisation (registration) holder

**Reason for transfer application:**

……
……
……
……

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

This file includes all the data in support of the original application together with all correspondence with the DDCR 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 (3)

## Requirements for Registration of Pharmaceutical Manufacturing Site

## (Site Master File)

1. The application has to be filled by the responsible pharmacist of the agent wholesaler or the local manufacturer.
2. A "Site Master File" for the manufacturing site containing the following information has to be attached:

Part One: **General information:**

1. Brief information on the firm (including name and address), relation to other sites and, particularly, any information relevant to understand the manufacturing operations.
2. Pharmaceutical manufacturing activities as licensed by the Competent Authorities.
3. Any other manufacturing activities carried out on the site.
4. Name and Exact Address of the Site, Including Telephone, Fax and twenty four hours Telephone Numbers.
5. Type of actual products manufactured on the site, and information about specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).
6. Short description of the site (size. location and immediate environment and other manufacturing activities on the site).
7. Number of employees engaged in the production, quality control, storage and distribution.
8. Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis.
9. Short description of the quality management system of the firm responsible for manufacture.

Part Two: **Personnel**:

1. Organisation chart showing the arrangements for quality assurance, including production and quality control.
2. Qualifications, experience and responsibilities of key personnel.
3. Outline of arrangements for basic and in-service training and how records are maintained.
4. Health requirements for personnel engaged in production.
5. Personnel hygiene requirements, including clothing.

Part Three: **Premises and equipment:**

1. Premises:
   - Simple plan or description of manufacturing areas with indication of scale.
   - Nature of construction and finishes.
   - Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for the manufacture of sterile products should be mentioned.
   - Special areas for the handling of highly toxic, hazardous and sensitizing materials.
   - Brief description of water systems (schematic drawings of the systems are desirable) including sanitation.
   - Maintenance (description of planned preventive maintenance programmes and recording system).

2. Equipment
   - Brief description of major production and control laboratories equipment (a list of equipment is not required).
   - Maintenance (description of planned preventative maintenance programmes and recording system).
   - Qualification and calibration, including recording system. Arrangements for computerized systems validation.

3. Sanitation
   - Availability of written specifications and procedures for cleaning manufacturing areas and equipment.

Part Four: **Documentation:**

1. Arrangements for the preparation, revision and distribution of necessary documentation for manufacture.
2. Any other documentation related to product quality which is not mentioned elsewhere (e.g. microbiological controls on air and water).

Part Five: **Production:**

1. Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters.
2. Arrangements for the handling of starting materials. Packaging materials, bulk and finished products, including sampling, quarantine, release and storage.
3. Arrangements for the handling of rejected materials and products.
4. Brief description of general policy for process validation.

Part Six: **Quality control:**

1. Description of the Quality Control system and of the activities of the Quality Control Department Procedures for the release of finished products.

Part Seven: **Contract manufacture and analysis:**

1. Description of the way in which the GMP compliance of the contract acceptor is assessed.

Part Eight: **Distribution, complaints and product recall:**

1. Arrangements and recording system for distribution.
2. Arrangements for the handling of complaints and product recalls.

Part Nine: **Self inspection:**

1. Short description of the self inspection system.