Palestinian National Authority
Ministry of Health

General Directorate of Pharmacy
Drug Control and Registration Dept

GUIDANCE ON PHARMACEUTICAL PRODUCTS REGISTRATION IN PALESTINE

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A MESSAGE FROM

HIS EXCELLENCY THE

MINISTER OF HEALTH

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Palestinian National Authority
Ministry of Health

Dear Colleagues,

I have the pleasure to introduce the first manual for the registration of pharmaceutical products in the Palestinian Ministry of Health (MOH). This manual will be used as a tool for good practices of the Ministry of Health (MOH) staff working on registration of pharmaceuticals. The manual will also be a useful tool for the pharmaceutical manufacturers and pharmaceutical vendors applying for registration.

This manual includes all procedures needed for registration for any pharmaceutical product, and was developed by the staff of the department for drug central and registration of the Ministry of Health (MOH) with technical support of the World Health Organization (WHO).

I hope that this undertaking will contribute to improving the the registration procedures of pharmaceutical products in a transparent and efficient manner.

Sincerely

Dr. Fathi Abu Moghli

Acknowledgments

The Palestinian Guidelines on Pharmaceutical Products Registration were prepared by the Palestinian Ministry of Health, Department of Drug Control and Registration Director, chemical Engineer Mohammad Mahareeq with the assistance of staff members, Pharmacist Majdi Abu-Hasan, Pharmacist Ghadeer Sanouri and Ms. Jamila Wasfi.
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1. Introduction:

The policy of the Ministry of Health is to ensure that all pharmaceutical products manufactured, imported or exported, distributed or sold in Palestine are of acceptable quality, safety and efficacy. The process of pharmaceutical products registration forms an important basis for evaluating and ensuring drug safety, efficacy and quality. Therefore, all drugs manufactured, imported/exported, distributed or sold in Palestine should be registered.

These objectives can be effectively achieved through:

a. Having in place a mandatory system of licensing of all medicinal products, whether locally manufactural or imported and licensing all local masnufacturers, importing and distributing agents.
b. Supervising all stages of manufacture and distribution of pharmaceutical products by appropriately qualified professional staff.
c. Complementing the registration system with an efficient system of inspection.
d. Enforcing the legislation.

The registration of drugs and related substances in Palestine is governed by the provisions of public health law (no. 20) and the Palestinian Pharmacy Practice Ordinance (no. 19).

This Drug Registration Guidance Document is developed to serve as the reference guide for applicants when applying for drug registration.

The Drug Control and Registration Department (DDCR) in the Ministry of Health is the organizational unit responsible for compliance and enforcement of this guidance, together with the Drug Technical Committee (DTC).

The Registration Guidance Document includes separate guidelines for registration of human drug products, separate guidelines for veterinary drug products and separate guidelines for cosmetic products.

2. Objectives:

The primary objectives of this guidance document are to provide transparent and clear guidelines and procedures for the registration of pharmaceutical products. including drugs for human use, drugs for veterinary use and cosmetic products, to ensure that all the products manufactured, imported, exported, distributed or sold in Palestine conform to acceptable standards of quality, safety and efficacy.

3. Organization and Personnel:

The overall responsibility for registration of pharmaceutical products is with the Director General of Pharmacy Department in the Ministry of Health The responsibility of the day-to-day registration and follow up activities is with the Director of the Department of Drug control and Registration (DDCR) of the Ministry of Health. The registration division is an integral part of the Department director.

A pre-requisite for joining the registration team is a scientific background with minimum first degree (B.sc) in different specialties in pharmacy, chemistry, microbiology etc.

Scientific and medical skills must be continuously updated to keep pace with drug discovery and development, including the development of new means of formulating, controlling and using well-established drugs. It is therefore essential that suitable training and practical experience be regularly offered to the staff concerned.

Training to gain experience may be done in different ways including:

- In-post training, which should include an element of apprenticeship gained through accompanying experienced staff.
- Participation in courses and seminars on relevant subjects.
- Updating knowledge in some areas including pharmaceutical technology, microbiology, pharmacology, quality control, etc.
- File evaluation and factual reporting skills.

The number of staff should be adequate to be able to fulfill their responsibilities. This is determined by many factors, including the number of products to be processed, the existence of local industry or not and the degree which the authority is prepared to rely on decisions made.

Pharmaceutical product registration staff should have the following personal qualities:

- Conforms to codes of ethics and conduct.
- Independence/no conflict of interest.
- No double role as registration staff and consultant.
- Able to withstand any attempts to influence decisions.
- Respectful of confidentiality rules.
- Impatrial: able to discharge regulatory responsibilities without fear or favor.

The functions of the registration staff shall include the following:

- Ensuring that all pharmaceutical products manufactured in, imported into or exported from Palestine conform to the standards of quality, safety, and efficacy.
- To grant, after assessment, licences for medicinal products, whether locally manufactured or imported.
- To cancel the registration of pharmaceutical products when their registration is not renewed on time, or when the continued use of which may be detrimental to public health.
- To maintain an inventory of registered pharmaceutical products.
- To publish lists of registered pharmaceutical products from time to time for public information.
- To ensure that registration files of pharmaceutical products are kept up to date by the applicants and to approve necessary alterations.
- To approve the use of unregistered pharmaceutical products for clinical trial purposes or use.
- To accumulate registration and application and renewal fees.
- Advise the Minister on matters concerning registration of medicinal products.

- To evaluate the prices of medicinal products and to publish price lists of registered products from time to time.
- To issue certificates of registration, certificates of pharmaceutical products (CPP) and certificates of free sale (FSC).
- To amend the registration rules and requirements as deemed necessary to keep pace with time demand(s).
- To cooperate with the Drug Technical Committee and other related committees in the registration, pricing and information issues.

4. Definitions:

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

1. **Accelerated stability studies:**
   Studies designed to simulate the rate of chemical and/or physical degradation of active ingredient or dosage form or product, under exaggerated storage conditions. The purpose is to determine the kinetic parameters, if possible and/or predict a tentative shelf life.
2. **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).
3. **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.
4. **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.
5. **Container labeling:**
   Means all information that appears on any part of a container, including that on any outer packaging such as a carton.
6. **Country of Origin:**
   It is the final location from which the finished product is dispatched after completing the final steps of manufacture.
7. **Drug, medicine or pharmaceutical product:**
   Means any substance or mixture of substances manufactured sold or represented for use in:

The diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical or mental state, or the symptoms thereof, in an humans or animals.

8. **Excipient:**

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

9. **Finished product:**

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

10. **Formulation:**

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

11. **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.

12. **Highly regulated countries:**

    Countries that are considered to be highly regulated. They include USA, E.U countries, Australia, Japan and Canada.

13. **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).

14. **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.

15. **Marketing authorization holder:**

    The company or drug store in whose name the marketing authorization (registration) has been granted. This party is responsible for all aspects of

product, including quality and compliance with the conditions of marketing authorization.

16. **Manufacturer:**

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

17. **Manufacture:**

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

18. **New Drug Product:**

    A drug containing an active ingredient, including its salts, esters, dervatives, etc, which is not a subject of current pharmacopeias.

19. **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**.**

20. **Pharmacopoeia:**

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

21. **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.

22. **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.

23. **Shelf life:**

    The period that product is expected to remain within specifications, as predicted from stability studies. The expiry date of an individual batch is based on the known shelf life.

24. **Stability:**

The capacity of an active ingredient or drug or dosage form to remain within specifications established to maintain its identity, purity, strength and other critical physico-chemical, microbiological and organoleptic properties during its shelf life.

25. **Storage condition:**

    The storage condition which shall guarantee the maintenance of the quality of the product in relation to its safety, efficacy and acceptability throughout the shelf life as may be predicted from the stability studies. The described conditions shall indicate temperature or temperature range in degree Celsius, humidity, light and other relevant conditions.

26. **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.

27. **Tentative shelf life:**

    A provisional shelf life predicted from results of accelerated stability studies.

28. **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 are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or in vitro studies.

5. 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 will have committed 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 Affairs 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 licence conditions, applicable legislation and guidelines.
10. Product registration shall be only through an authorized agent, exclusive distributor, scientific office or local manufacturer.
11. The registration documents shall be submitted in bound files; pages shall be numbered and the file should have 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, to be determined by the Minister of Health.

19. The DDCR will charge the applicant any costs for carrying out laboratory testing related 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, the applications should include 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 to 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 inserts must be amended to include any new adverse reactions, warnings, precautions 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 re-registered 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 will 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 are 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 whereby 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. These 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. A 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 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.

PART I

GUIDELINES OF HUMAN MEDICINAL PRODUCTS REGISTRATION IN PALESTINE

Section One: General Instructions for registration of Medicinal Products:

In addition to general registration provisions, the following are applicable for registration of medicinal products:

1. The requirements are applicable to the following categories of medicinal products:
   1.1. Generic medicinal products.
   1.2. Pharmacopoeial products including (BP, Eur. P, USP, JP, Int. Ph.).
   1.3. New drug products
2. All registration processes should be done by pre-licensed medicinal authorization holder(s), as required by the Ministry of Health regulations.
3. The following documents are required to be submitted with the registration file, for the registration of imported medicinal products:
   3.1. The valid licence drug store/wholesaler or scientific office issued from the Ministry of Health.
   3.2. 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.
   3.3. An authorization for registration from the product owner.
   3.4. An authenticated certificate of pharmaceutical product (CPP) issued from the responsible health authorities of the producer`s country of origin.
   3.5. A valid GMP certificate issued from the responsible health authorities of the producer`s country of origin.
   3.6. A valid and authenticated free sale certificate of the product issued by the responsible health authority of the producer`s country of origin if the CPP not provided..

3.7. All the above-mentioned documents should be authenticated by the Palestinian embassy in the country of origin.

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

3.9. The prices certificates as required in the pricing policy document.

4. A pre-approval application for registration, submitted in five copies to the DDCR. The product pre-approval should be approved before preceding the registration process.
5. An application for registration filled by the responsible pharmacist and submitted in five copies to the DDCR.
6. An application for a quality control certificate, submitted in three copies to the DDCR.
7. The following documents shall be submitted in addition to the registration requirements <u>for products to be manufactured under licence (contract manufacturer):</u>

   7.1. An authenticated manufacturing licence for the product owner, issued from the relevant health authorities in the country of origin.

   7.2. A legalized letter of agreement between the two concerned parties, signed by both parties, and issued in accordance with the GMP requirements.

   7.3. The plant master file for the contract giver and acceptor .

   7.4. An authenticated GMP certificate issued from the relevant health authorities for both parties .

   7.5. An original authenticated free sale certificate/CPP issued for the concerned product which is under contract, from the relevant health authorities.
8. Bioequivalent study (where applicable) from local generic manufacturers and countries which are not considered highly regulated.

Section Two: Contents of chemical and pharmaceutical data

The material should be submitted in a combined hard cover file. The following should 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 medicinal products)**. The file should have protruding dividers, each bearing the name of the relevant section.

Documents required to be in the registration file:

1. **Table of contents.**

2. **The complete and accurate composition of the product, active and inactive ingredients whether they appear in the final product or not**:
   - Quantities should be in unit per dose.
   - The composition should be formatted as below:

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

   - The formula 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, 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. **Chemical, Pharmaceutical and biological documents**:
   Monographs of active ingredient(s).
   The monographs on pharmacopoeial active ingredient(s) shall include the following:
   - The International Non-propriety Name (I.N.N).
   - Structural formula.
   - Specifications.
   - Method(s) of analysis.
   - Source of supply including the name & address of the manufacturer.

- Certificate of analysis from the manufacturer.
- Photocopy of the pharmacopoeial reference.

Drug master file (DMF) for non-pharmacopoeial active ingredient(s) including the following::

- The International Non-propriety Name (I.N.N).
- Description of the active material.
- Chemical & physical & microbiological (where applicable) specifications.
- Methods of analysis.
- Structural formula & molecular weight.
- Source of supply including the name & address of the manufacturer.
- Purity tests.
- Impurities, and degradative products.
- Identification tests.
- Certificate of analysis from the manufacturer.
- Safety data sheet and isomers.

Monographs of the inactive ingredients which must have the same information of the active ingredients.

For capsules, a certificate issued from the Ministry of Health of the exporting country assuring the freedom of the capsules from BSE/TSE.

5. **Method of preparation**:

The document should have the following information:

- Master formula including complete composition of active ingredient/s and inactive ingredient/s. The quantities must be presented in both per unit dose and per batch. Yield and acceptable limits must be included.
- Step by step manufacturing procedure including in-process controls. The flow chart of the manufacturing procedure should be included.
- Process validation. Including experimental data showing that the manufacturing process, using stated quality and types of equipment specified, is a suitable one and will consistently yield a product of the desired quality.

6. **Specifications of the packaging materials (primary and secondary) including:**

- The designated name of material and internal code reference.
- Qualitative and quantitative requirements with acceptance limits.
- The design layout.
- Composition of the packaging materials.
- Quality control testing.
- Supplier(s) of the primary packaging materials.

7. Packaging procedure:
Packaging instructions including description of the packaging steps and measures for control during packaging procedure.

8. In-process control:
The documents must include:

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

9. Pharmacotechnical data (**Finished product specifications**):

- Specifications of the finished product including their reference(s).
- In addition to the other requirements, for non-pharmacopoeial products the followings should be submitted:
  - Dissolution comparison profile with innovator product & the calculation of similarity factor in 3 medias (where applicable).
  - Samples from innovator product.
  - A description of the methodology for determinig product specifications.
- The department is entitled to require, at any time, additional data and the performance of further tests, depending on the nature of the medicinal product.
- Below are the details of the data to be supplied. Parameters marked with asterisks are to be tested within the framework of 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 determination with 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 & Elixirs)

- 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.

10. Quality control of the finished product

10.1. The 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 (where applicable).

10.2. A photocopy of the monograph should be attached, stating the name of the pharmacopoeia used and the edition.

10.3. Analytical validation for non-pharmacopoeial methods.

11. Certificate of analysis for the finished product:

A certificate of analysis for the finished product with all results of 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.

12. Stability Study:

12.1. 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 ome general requirements for stability study testing.

12.2. Stability studies should investigate:

12.2.1. The stability of the drug in unopened packs.
12.2.2. Stability of the drug following manipulation necessary prior to administration (e.g. reconstitution or dilution).
12.2.3. Stability of the drug during use (e.g. the effects of opening and closing of the container closure system)

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

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

12.5. 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.

12.6. Data 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.

12.7. 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.

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

12.9. 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 tesing period.

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

12.10.1. General case

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60% RH ± 5% RH or 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.

12.10.2. 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 or 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.

12.10.3. 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

12.10.4. 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

12.11. 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:
12.11.1. The shelf-life may be extended on the basis of real-time stability studies carried out for the full shelf-life period.
12.11.2. An extension shall never be based on accelerated studies.
12.11.3. The shelf-life of a product may not exceed five (5) years.

12.12. 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:
12.12.1. Chemical stability of the active ingredient and any essential excipients (e.g. preservatives and antioxidants.)
12.12.2. Degradation product levels.
12.12.3. Physical properties (e.g. particle size, dissolution, hardness, viscosity, re-suspendability etc)
12.12.4. Packaging interactions and integrity.
12.12.5. Microbiological stability (including anti-microbial preservative efficacy).
12.12.6. Organoleptic properties (odour, taste, ..etc).

12.13. The detailed requirements of the 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 refer to these guidelines for performing stability studies.

13. Patient Package Insert:

Each application must be accompanied by proposed information for the patient. The package insert shall be written in a simple language, comprehensible to the layman reading it.

Pictograms (small pictures describing, in graphic form, instructions and/or warnings relevant to the use of the medicinal product) may be added, following approval of the "DDCR".

The patient insert must be written in Arabic & English language and includes the followings:

- **Product name and dosage form.**
- **Composition** *(Provide the name/s of the active ingredient/s and their quantity/concentration). For a product containing ingredients such as sugar, sodium, aspartame, etc.,their content should be stated per unit dose. For a product which does not require a doctor's prescription (OTC), complete disclosure of the inactive ingredients must be made, in descending order of their quantity .*
- **Therapeutic activity** *(A brief explanation of the activity and mode of action of the drug in a language that is understandable to the patients).*
- **Approved indication** *(for OTC medicinal products).*
- **When the preparation should not be used** *(for e.g. don't use this product if you are pregnant or breast feeding, if you have G6PD deficiency enzyme, etc.)* **When applicable**.
- **Do not take this medicine without consulting a doctor before starting treatment** *(if you are pregnant, breast feeding, impaired kidney function, Asthma, heart problems etc).* **When applicable**.
- **How will this medicine affect your daily life** *(for e.g. Use of this medicine may impair your alertness, don't drink alcoholic beverages, sensitivity to sun).*
- **Warnings** *(Prolonged use may cause dependence, may cause blurring of vision, may affect some lab tests, etc.)*
- **Drug interactions** *(inform your doctor if you take any medicine or you just finished taking it to prevent hazard or lack of efficacy arising from drug interaction).*
- **Overdose.**
- **Side effects** *(e.g. dryness of the mouth, constipation, diarrhea, nausea….etc).*
- **Recommended dosage unless otherwise prescribed by your doctor:** *(for prescription, only medicine) the statement "dosage is according to physician instructions only" should be added before stating the usual dose).*
- **Attention** *(e.g. don't swallow, for external use only etc).*
- **How you can contribute to the successful of treatment.**

- **Direction for use** *(e.g. dilute with water, shake well before use).*
- **Storage** *(e.g. store in a cool place, dark, dry, in a refrigerator).*
- **Presentation.**
- **Name and address of manufacturer/ Importer**.

14. Prescribing information for physician (Clinical & Toxicological Data):

If the product is declared to be dispensed without prescription (OTC drug), the prescriber information is not required.

The information shall be submitted in Arabic or English language and shall include the following sections:

- Composition: The active ingredient/s and its quantity per unit dose and a list of the inactive ingredient present in the medicinal product in decreasing order of quantity.
- Therapeutic class.
- Dosage form.
- Mechanism of action.
- Pharmacokinetics.
- Indication/s.
- Contraindications.
- Warning including data on teratogenecity, use in pregnancy, use in breast feeding, use in pediatrics, use in elderly, use in patients with impaired organ function (kidney, liver, etc.)
- Adverse reaction.
- Precautions including drug and diagnostic interactions.
- Dose and administration.
- Overdose- manifestations and treatment.
- Copy of references from where the information were collected must be attached to the prescribing information..

15. Packaging and labeling (Includes the primary and secondary packaging material).

A sample from the secondary packaging materials shall accompany the application, or clear artworks of the secondary packaging materials showing the required information and the original colours used in the materials. Both the inner and outer label of the packaging material should contain the following information:

- Trade name of the product in Arabic and English.
- Generic name: the chemical name, printed in Latin letters.
- Pharmaceutical dosage form and strength.
- Name and address of the manufacturer in Arabic/English.
- Name and address of the importer in Arabic/ English(For imported drugs).
- The logo of the manufacturer.
- Volume/weight (Net content).
- The active ingredient and their quantities per unit dose of the product, in their generic name, in Latin letters and where there is no generic name, the chemical name.
- 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, prescription only medicine …etc).
- Special warning statements for adaptation and for alertness and driving shall appear on labels and cartons in the cases of narcotic and dangerous products.
- For medicinal products containing aspartam, sugar or sodium warning statements for patients shall be added on the label, carton and patient inserts.

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 suppliers.
- Storage conditions.
- The procedure for taking packaging samples for analysis.
- Specifications of the packaging material in immediate contact with the medicinal product shall include (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).
- The package must include the patient leaflet printed in Arabic and English, with all the information mentioned in (Section 2, Point 9).
- The blister must have the following information printed on it:
- The brand name.
- Generic name(s) for less than three ingredients.
- Expiry date.
- Batch number.
- Company name

If the Imported product is packed in a site which is different from the site of production, names and addresses of both sites should be stated on the package of the product and on the submitted registration documents.

Quality Control & Registration Department reserves the right to stipulate further requirements if appropriate.

Section Three: Registration of new drug product:

New drug products can be registered after fulfilling the following conditions:

1. The product shall be registered in one of highly regulated countries (USA, European, Union, Canada, Australia, Japan).

2. The product shall be registered in one of the reighbouring countries (Jordan, Saudi Arabia, Israel).

3. Submission of a file containing a summary of clinical and toxicological data and information.

4. Chemical, microbiological and pharmaceutical data as mentioned in section two.

Section Four: Renewal of registration:

1. Application for renewal of registration shall be submitted to the Drug Control and Registration –MOH 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.
   - 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 constituent(s).

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.

Section Five: Amendment to the registration of a medicinal product:

Amendments to the registration of a 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(s) (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 reserves the right to require additional data or waive any of the above requirements.

Section Six: Bioavailability/Bioequivalence Testing in Humans (In-VIVO)

1. Definition of bioavailability:
   The rate and extent of availability of an active drug ingredient from a dosage form as determined by its concentration/time curve in the systemic circulation or by its excretion in urine, when more than 80% of the excretion of the active material is via the urine.

2. General Instructions:
   2.1. The following shall be submitted concerning the centre in which the study was conducted:
      2.1. An authenticated licence issued from the relevant health authorities.
      2.2. An authenticated certificate from the relevant health authorities inside the country or from an international health organization;

indicating the compliance of the centre with the Good Clinical Practices (GCP) and the Good Laboratory Practices (GLP).

2.2. The submitted file shall be original and the name and the address of the centre shall be clear in the file.

2.3. The study file shall include the name of the principle investigator, his/her address and the contact telephone number(s) / E-mail.

2.4. The submitted file shall include:

4.1. The study protocol.

4.2. The analytical method(s) & validation.

4.3. A summary of the calculation(s) method(s) which were used in the evaluation of the results.

2.5. The file shall include the clinical tests for the persons who were included in the study.

2.6. The study shall be conducted on the product manufactured in the approved site of manufacturing that belongs to the company applying for registration.

2.7. A study to determine Bioequivalence shall be performed by a licensed centre known to ber reliable.

2.8. The bioequivalent study must be done on the generic product compared to the innovator product.

2.9. The innovator product shall be of the same dosage form & the same strength.

2.10. The Bioequivalence study of medicinal product in human shall be performed with the approval of the Helsinki Ethical Committee of the hospital and the Ministry of Health and with written informed consent of each participant in the study.

2.11. The size of the study groups shall be determined by accepted standards of biostatistics, in order to ensure unequivocal results. In general not less than (16) participants are required for each group. However, this number will not be necessarily sufficient in every case. A medicinal product for which substantial inter subject variability and/or a narrow therapeutic window exist, will require a larger number of volunteers.

2.12. The design of the study shall be cross-over, in healthy volunteers. The Bioavailability/ Bioequivalence study shall be done on ages between 18-55 years of both sexes, except where this is not possible for medical reasons.

2.13. The following shall be excluded from such studies - volunteers who smoke or habitually consume alcohol, those who are taking medication on a regular basis and female volunteers using the contraceptive pills. Verification of these exclusion criteria shall be recorded in the report for each volunteer.

2.14. The Bioavailability / Bioequivalence shall be performed in the fasting state, unless the medicinal product is intended for administration after a meal. The fasting period shall be determined by the conditions of the trial. When the study is conducted following the consumption of food the content of the meal taken during the study shall be detailed.

2.15. The timing of blood sampling (and/or collection of urine specimens) following administration of the medicinal product is a function of the pharmacokinetic properties of the medicinal product under study. As a rule, all the tests are to be performed within 3-5 half-life periods at the drug clearance stage. Thus the area-under-the-curve (AUC) observed in the population will represent at least 80% of the total AUC following extrapolation to infinity.
In the case of a sustained-release medicinal product the study period shall be extended by a further 12 hours, in order to cover the increased release and absorption periods. For a sustained-release medicinal product, or a medicinal product possessing non-linetics-the bioavailability shall also be tested with a repeat dose until steady state has been achieved. The test is to be conducted by comparison with the steady-state of the standard.

2.16. Bioavailability studies of medicinal products which might have significant toxicological effects (such as oncologicals, narcotics etc.), shall be conducted in patients as part of their treatment schedule.

2.17. Prior to conducting a bioavailability study for the purpose of registering a medicinal product, the study protocol may be submitted to the pharmaceutical administration for appraisal. Adopting such a course of action shall not guarantee ultimate approval of the study results.

2.18. The DDCR is entitled to require of a manufacturer/importer submission of results of additional bioavailability studies, at its discretion.

2.19. The study report and its results shall include, inter alia, the following data:

- 2.19.1. An up-to-data review of the pharmacokinetics of the medicinal product under examination.
- 2.19.2. The name of the medicinal product studied, the name of the manufacturer, the manufacturing site (which must be the same as that defined in the registration application), composition (including certificate of analysis), batch number and size, production date and expiry date, and a declaration stating that the said batch is a routine production batch.
- 2.19.3. A declaration stating that the tests were carried out against the standard.
- 2.19.4. With regard to the standard, the name of the manufacturer, manufacturing site, batch number, place or purchase and expiry date shall be recorded.
- 2.19.5. The name of the investigator who carried out the study and where it was conducted, together with an authorization from the Helsinki Committee.
- 2.19.6. Results of analysis of variance, ANOVA (as the primary test.)
- 2.19.7. Clinical and laboratory data for each volunteer-such as age, weight, height, results of blood and urine tests etc.
- 2.19.8. Date of testing for each volunteer.
- 2.19.9. Details of side effects observed during the study.
- 2.19.10. Validation of the methodology-method of analysis of the results and their statistical significance.

2.20. In special cases, In-vitro tests may be acceptable in order to establish Bioequivalence for products of the same manufacturer containing the same active ingredient(s) in the same dosage form but in different strength; provided the following conditions:
- ❖ Identical relative proportions between the active and non-active ingredients for the two products.
- ❖ Proof of Bioequivalence for the higher strength product.
- ❖ The two products are shown to be equivalent In-vitro dissolution tests.
- ❖ Linear kinetics exist within the limits of recommended dosage.
- ❖ Convincing correlation has been demonstrated between the results of In-vitro tests for the first product and In-vitro data in other formulation.

2.21. The DDCR reserves the right to exempt any product from the Bioavailability/ Bioequivalence study according to the WHO "Guidelines on registration requirements to establish interchangeability". WHO Technical Report Series, No. 937, 2006.

2.22. Guidelines for bioavailability and Bioequivalence studies are illustrated in details in ***Appendix (5)***

Section Seven: Application Forms

1. Pre approval application for medicinal product registration
2. Registration Application Form
3. Application form for a quality control certificate
4. Amendments application form

5. Registration renewal application form

Pre-Approval Application for Medicinal Product Registration

To: The director of Drug Control and Registration Department

I hereby request your agreement to register the following medicinal product:-

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

2. **Medicinal product:**
   Suggeted Name(s) of the product:

…….
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 ( ) Human 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 the Reg. division **Director of DDCR**

Date: **Date:**

Registration Application Form

To: The Director of Drug Control and Registration Department

I hereby request that the following medicinal products be registered in the drug register

1. Registration applicant:

Name of the Applicant (Responsible Pharmacist): .....
Address:
.....
.....
.....……

2. Medicinal product:

Name of product: .....
Dosage form : .....
Packaging: .....
Strength: .....

3. Manufacturer :

Name: .....
Address: .....
Address of the supplier branch in Palestine (in case of imported drugs):
……
……
……
……

4. Purpose of registration :

( ) Manufacturing & Marketing ( ) Importing & Marketing ( ) Packaging & Marketing ( ) Human 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:

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

(Note: **a.** Name of the method & reference should be mentioned for both in-process & finished product analysis.
b. Qualitative & quantitative analytical procedures for the finished product should be attached to the application).

9. Containers:

Type and size(s) of container used for packaging the product :
Primary: .....
Secondary: .....

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 Composition (Active ingredient(s) and their quantities):

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

11.2 Theraputic activity:

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

11.3 Indications:

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

11.4 Contraindications:

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

11.5 Warning:

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

11.6 Drug interactions:

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

11.7 Side effects:

.....

.....
.....

11.8 Directions for use:

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

11.9 Adverse reactions and drug interactions in children and infants:

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

11.10 Recommended dosage:

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

11.11 Route(s) of administration:

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

11.12 Storage conditions:

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

12. Clinical use:

12.1 Pharmacological action and recommended clinical use :

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

12.2 Proposed route(s) of administration:

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

12.3 Recommended dosage:

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

13. Toxicology (Pathology, toxicology, teratology): -

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

Signature of the responsible pharmacist **Date**

…… **……**

****

For the use of Drug Technical Committee

14. Approval of registration :

14.1 Marketing restriction: ( ) Prescription-only medicine ( ) For hospital use only
( ) Other restrictions:.....

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

14.3 Warning that shall appear on the label/ package
( ) Prescription only medicine ( ) Toxica ( ) Seperanda
( ) for external use ( ) Shake before use
( ) Caution ! use may impair driving ability
( ) Other warning or statement/s may be required for this product: .....
.....
.....

14.4 Shelf life: ……..

14.5 Registration number: .....

14.6 Registration valid from ..... To .....

14.7 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:……,

Application Form for a Quality Control Certificate:

To: The Director of Drug Control and Registration Department

We hereby request that the following 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:……

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 Product (CPP).
( ) Patient 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 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 physician & references.
( ) 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.
( ) Bioequivalence file (where applicable).
( ) In-vitro equivalency (where required).
( ) Summary of clinical and toxicological data for new products.

Signature …….. Date ……..

Registration Renewal Application Form

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

- **Applicant information**:
  - Applicant Name (responsible pharmacist) :…….
  - 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 **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:……

Amendments Application Form

To: The Director of Drug Control and Registration Department

We hereby request the approval of the changes/variations mentioned below

Details of the current registration:

- Name of the 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 origin.

  ……
  ……
  ……

Declaration of the applicant:

I hereby declare that:

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

☐ All conditions 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 receipt of the application:…….…….
- Name of the receiver:…….……
- Ammendment decision:

  ☐ The requested amendment(s) is approved.

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

  1. …….
  2 ……...
  3. …….

  ☐ Other: the applicant is requested to:

……
……
……

…… ……..

Head of the registration division Director of DDCR

Section Eight: 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

4. **Appendix (4):** Guidelines for Bioavailability and Bioequivalence studies

Appendix (1)

File Requirements for Variations (Amendments)

1.	**Change or inclusion of manufacturer of active pharmaceutical ingredient (API)**	
	Documentations 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:** **2.1. No change in the manufacturing process and in the release and shelf life specifications, including test methods** **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.
	Documentations 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** documentations 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.
	Documentations 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 conformity to the current shelf life specification.
	Documentations 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 conformity to the current shelf life specification.
	Documentations 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 conformity to the current shelf life specification for the reconstituted product.
	Documentations 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.
	Documentations 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.

	Documentations 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.
	Documentations 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);
	Documentations 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.
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**	
	Documentations 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
	Documentations 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.
	Documentations 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.
	Documentations 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	
	-	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.
	Documentations 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.** **18.1 Specification limits are tightened** **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.
	Documentations 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 documentations 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.
	Documentations 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 Pharmacopoeia;
	-	Exclude the change from one pharmacopoeia to another.
	Documentations 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
	Documentations 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).
	Documentations 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** **23.1 Conventional dosage form, suppositories and pessaries** **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).
	Documentations 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 documentations 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 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.
	Documentations 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.
	Documentations 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 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.
	Documentations 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 approved for pharmaceutical use;
	-	The release and shelf life specifications of the drug product have not changed, except for the change in flavour.
	Documentations 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 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.
	Documentations 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**	
	Documentations 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.
	Documentations 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.
	Documentations 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.
	Documentations 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);
	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.
	Documentations 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.
	Documentations 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** **35.1 Specification limits are tightened** **35.2 Addition of new test parameter and limits**	
	Documentations 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** documentations 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;
	Documentations 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** **37.1 Specification limits are tightened** **37.2 Addition of new test parameter and limits**	

	Documentations 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 documentations 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.
	Documentations 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.
	Documentations 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**	
	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.
	Documentations 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.
	Documentations 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.
	Documentations 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: • **Addition/deletion of bar code** • **Replacement of distributor details** • **Layout without altering text or meaning** • **Deletion of indication** • **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.
	Documentations to be submitted	
	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.

	Documentations 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 authorizations

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 amendments 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 authorization (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 authorization (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 made 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 necessary 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:
   1.1. Simple plan or description of manufacturing areas with indication of scale.
   1.2. Nature of construction and finishes.
   1.3. 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.
   1.4. Special areas for the handling of highly toxic, hazardous and sensitizing materials.
   1.5. Brief description of water systems (schematic drawings of the systems are desirable) including sanitation.
   1.6. Maintenance (description of planned preventive maintenance programmes and recording system).

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

3. Sanitation
   1.10. 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.

Appendix (4)

Guidelines for Bioavailability & Bioequivalence Studies

Contents

1. INTRODUCTION

Ensuring uniformity in standards of quality, efficacy and safety of pharmaceutical products is the fundamental responsibility of DDCR. Reasonable assurance has to be provided that various products, containing same active ingredients, marketed by different marketing authorization holders, are clinically equivalent and interchangeable.

Both bioavailability and bioequivalence focus on the release of a drug substance from its dosage form and subsequent absorption into the systemic circulation. For this reason, similar approaches to measuring bioavailability should generally be followed in demonstrating bioequivalence.
Bioavailability can be generally documented by a systemic exposure profile obtained by measuring drug and/or metabolite concentration in the systemic circulation over time. The systemic exposure profile determined during clinical trials in the early drug development can serve as a benchmark for subsequent BE studies.

Bioequivalence studies should be conducted for the comparison of two medicinal products containing the same active substance. The studies should provide an objective means of critically assessing the possibility of alternative use of them. Two products marketed by different licencees, containing same active ingredient(s), must be shown to be therapeutically equivalent to one another in order to be considered interchangeable. Several test methods are available to assess equivalence, including:

i. Comparative bioavailability (bioequivalence) studies, in which the active drug substance or one or more metabolites is measured in an accessible biological fluid such as plasma, blood or urine
ii. Comparative pharmacodynamic studies in humans
iii. Comparative clinical trials
iv. In-vitro dissolution tests

For classes of products, including many biologicals such as vaccines, animal sera, and products derived from human blood and plasma, and product manufactured by biotechnology, the concept of interchangeability raises complex issues which may be addressed by the applicant on the basis of contemporary scientific rationale.
In vivo bioequivalence/bioavailability studies recommended for approval of modified release products should be designed to ensure that:

i. The product meets the modified release label claims.
ii. The product does not release the active drug substance at a rate and extent leading to dose dumping.
iii. There is no significant difference between the performance of the modified release product and the reference product, when given in dosage regimes to arrive at the steady state.
iv. There must be a significant difference between the performance of modified release product and the conventional release product when used as reference product.

2. DEFINITIONS

BIOAVAILABILITY:
The rate and extent of availability of an active drug ingredient from a dosage form as determinal by its concentration/time curve in the systemic circulation or by its excretion in urine, when more than 80% of the excretion of the active material is via the urine.

BIOEQUIVALENCE:
PHARMACEUTICAL ALTERNATIVES
Bioequivalence of a drug product is achieved if its extent and rate of absorption are not statistically significantly different from those of the reference product when administered at the same molar dose.

CLINICAL TRIAL:
A clinical trial is a systematic study of pharmaceutical products in human subject(s), in order to discover or verify the clinical, pharmacological (including pharmacodynamic / pharmacokinetic), and/or adverse effects, with the object of determining their safety and/or efficacy.

MODIFIED RELEASE DOSAGE FORMS:
Modified-release dosage forms are those for which the drug-release characteristics of time course and/or drug-release location are chosen to accomplish such therapeutic or convenience objectives that are not offered by immediate-(conventional) release dosage forms.

PHARMACEUTICAL EQUIVALENTS:
Pharmaceutical equivalents are drug products that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients.

PHARMACEUTICAL ALTERNATIVES :
Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester.

PHARMACODYNAMIC EVALUATION:
Pharmacodynamic evaluation is measurement of the effect on a pathophysiological process as a function of time, after administration of two different products to serve as a basis for bioequivalence assessment.

PHARMACOKINETICS:
Pharmacokinetics deals with the changes of drug concentration in the drug product and changes of concentration of a drug and/or its metabolite(s) in the human or animal body following administration of the drug product, i.e. the changes of drug

concentration in the different body fluids and tissues in the dynamic system of liberation, absorption, distribution, body storage, binding, metabolism, and excretion.

REFERENCE PRODUCT:
A reference product is a pharmaceutical product intended to be interchangeable with the new product in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available the product which is the market leader may be used as a reference product, provided it has been authorized for marketing and its efficacy, safety has been established and documented.

SUPRA-BIOAVAILABILITY:
This is a term used when a test product displays an appreciably larger bioavailability than the reference product.

SUSTAINED RELEASE DOSAGE FORM:
These are modified release dosage forms where the liberation (drug release) rate constant is smaller than the unrestricted absorption rate constant.

STEADY STATE:
Steady state is the state when the plasma concentration of drug at any time point during any dosing interval should be identical to the concentration at the same time during any other dosing interval. The steady state drug concentrations fluctuate (oscillate) between a maximum and a minimum steady state concentration within each of the dosing intervals.

THERAPEUTIC EQUIVALENTS
Therapeutic equivalents are drug products that contain the same active substance or therapeutic moiety and, clinically show the same efficacy and safety.

GENERIC PRODUCT:
A pharmaceutical product, usually intended to be interchangeable with innovator product which is usually manufactured without a licence from the innovator company and marketed after expiry of patent or other exclusivisty rights.

INNOVATOR PHARMACEUTICAL PRODUCT:
Generally, the innovator pharmaceutical product is that which was first authorized for marketing, (normally as a patented drug) on the basis of documentation of efficacy, safety and quality (according to contememporary requirements). When drugs have been available for many years, it may not be possible to identify an inovvator pharmaceutical product.

INTERCHANEABLE PHARMACEUTICAL PRODUCT:
An interchangeable pharmaceutical product is one which is therapeutically equivalent to a reference product.

MULTISOURCE PHARMACEUTICAL PRODUCTS:
Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchaneable.

PHARMACOKINETIC TERMS

C_{max}
This is the maximum drug concentration achieved in systemic circulation following drug administration.

C_{min}
This is the minimum drug concentration achieved in systemic circulation following multiple dosing at steady state.

C_{pd}
This is the pre-dose concentrations determined immediately before a dose is given at steady state.

T_{max}
It is the time required to achieve maximum drug concentration in systemic circulation.

AU C_{0-t}
Area under the plasma concentration - time curve from 0 h to the last quantifiable concentration to be calculated using the trapezoidal rule

$AUC_{0-\infty}$
Area under the plasma concentration - time curve, from zero to infinity to be calculated as the sum of AUC0 plus the ratio of the last measurable concentration to the elimination rate constant

AUC_{0-T}
Area under the plasma concentration - time curve over one dosing interval following single dose for modified release products.

$AUC_{0-T(SS)}$
Area under the plasma concentration - time curve over one dosing interval in multiple dose study at steady state.

K_{el}
Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve.

$T_{1/2}$
Elimination half life of a drug is the time necessary to reduce the drug concentration in the blood, plasma, or serum to one-half after equilibrium is reached.

3. SCOPE OF THE GUIDELINES:

Bioavailability and Bioequivalence studies are required by regulations to ensure therapeutic equivalence between a pharmaceutically equivalent test product and a reference product. Several in vivo and in vitro methods are used to measure product quality.

3.1. When bloequivalence studies are necessary and types of studies required.

3.1.1. In vivo studies:

For certain drugs and dosage forms, in vivo documentation of equivalence, through either a bioequivalence study, a comparative clinical pharmacodynamic study, or a comparative clinical trial, is regarded as especially important. These include:

a. Oral immediate release drug formulations with systemic action when one or more of the following criteria apply:
   i. Indicated for serious conditions requiring assured therapeutic response;
   ii. Narrow therapeutic window/safety margin; steep dose-response curve;
   iii. Pharmacokinetics complicated by variable or incomplete absorption or absorption window, nonlinear pharmacokinetics, pre-systemic elimination/high first-pass metabolism >70%;
   iv. Unfavourable physicochemical properties, e.g., low solubility, instability, meta-stable modifications, poor permeability, etc.;
   v. Documented evidence for bioavailability problems related to the drug or drugs of similar chemical structure or formulations;
   vi. Where a high ratio of excipients to active ingredients exists.
b. Non-oral and non-parenteral drug formulations designed to act by systemic absorption (such as transdermal patches, suppositories, etc.).
c. Sustained or otherwise modified release drug formulations designed to act by systemic absorption.
d. Fixed-dose combination products with systemic action.
e. Non-solution pharmaceutical products which are for non-systemic use (oral, nasal, ocular, dermal, rectal, vaginal, etc. application) and are intended to act without systemic absorption. In these cases, the bioequivalence concept is not suitable and comparative clinical or pharmacodynamic studies are required to prove equivalence. There is a need for drug concentration measurements in order to assess unintended partial absorption.

Bicequivalence documentation is also needed to establish links between:

i. Early and late clinical trial formulations.
ii. Formulations used in clinical trials and stability studies, if different.
iii. Clinical trial formulations and to be marketed drug products.
iv. Other comparisons, as appropriate

In each comparison, the new formulation or new method of manufacture shall be the test product and the prior formulation (or respective method of manufacture) shall be the reference product.

3.1.2. In vitro studies:

In following circumstances equivalence may be assessed by the use of in vitro dissolution testing:

a. Drugs for which the applicant provides data to substantiate all of the following:
   i. Highest dose strength is soluble in 250 ml of an aqueous media over the pH range of 1-7.5 at 37°C.
   ii. At least 90% of the administered oral dose is absorbed on mass balance determination or in comparison to an intravenous reference dose.
   iii. Speed of dissolution as demonstrated by more than 80% dissolution within 15 minutes at 37°C using IP apparatus 1, at 50 rpm or P apparatus 2, at
   100 rpm in a volume of 900 ml or less in each of the following media:
      1. 0.1 N hydrochloric acid or artificial gastric juice (without enzymes)
      2. 2. a pH 4.5 buffer
      3. 3. a pH 6.8 buffer or artificial intestinal juice (without enzymes)

b. Different strengths of the drug manufactured by the same manufacturer, where all of the following criteria are fulfilled:
   i. The qualitative composition between the strengths is essentially the same;
   ii. The ratio of active ingredients and excipients between the strengths is essentially the same, or, in the case of small strengths, the ratio between the excipients is the same;
   iii. The method of manufacture is essentially the same;
   iv. An appropriate equivalence study has been performed on at least one of the strengths of the formulation (usually the highest strength unless a lower strength is chosen for reasons of safety); and
   v. In case of systemic availability - pharmacokinetics have been shown to be linear over the therapeutic dose range.
   In vitro dissolution testing may also be suitable to confirm unchanged product quality and performance characteristics with minor formulation or manufacturing changes after approval.

3.2. When bloequivalence studies are not necessary:

In following formulations and circumstances, bioequivalence between a new drug and the reference product may be considered self-evident with no further requirement for documentation:

a. When new drugs are to be administered parenterally (e.g., intravenous, intramuscular, subcutaneous, intrathecal administration etc.) as aqueous solutions and contain the same active substance(s) in the same concentration and the same excipients in comparable concentrations;
b. When the new drug is a solution for oral use, and contains the active substance in the same concentration, and does not contain an excipient that is known or suspected to affect gastro-intestinal transit or absorption of the active substance;
c. When the new drug is a gas;
d. When the new drug is a powder for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above;

e. When the new drug is an otic or ophthalmic or topical product prepared as aqueous solution and contains the same active substance(s) in the same concentration(s) and essentially the same excipients in comparable concentrations;
f. When the new drug is an inhalation product or a nasal spray, tested to be administered with or without essentially the same device as the reference product, prepared as aqueous solutions, and contain the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations. Special in vitro testing is required to document device performance comparison between reference inhalation product and the new drug product.
g. When the new drug products are topical products prepared as qgueous solutions and contain the same active ingredient(s) in the same concentration and the same excipients in comparable concentrations.

For (e) and (f) above, the applicant is expected to demonstrate that the excipients in the new drug are essentially the same and in comparable concentrations as those in the reference product. In the event this information about the reference product cannot be provided by the applicant, in vivo studies need to be performed.

4. DESIGN AND CONDUCT OF STUDIES

4.1. Pharmacokinetic Studies:

4.1.1. Study Design:

The basic design of an in-vivo bioavailability study is determined by the following:

i. What is the scientific question(s) to be answered.
ii. The nature of the reference material and the dosage form to be tested.
iii. The availability of analytical methods.
iv. Benefit-risk ratio considerations in regard to testing in humans.

The study should be designed in such a manner that the formulation effect can be distinguished from other effects. Typically, if two formulations are to be compared, a two-period, two-sequence crossover design is the design of choice with the two phases of treatment separated by an adequate washout period which should ideally be equal to or more than five half life's of the moieties to be measured.

Alternative study designs include the parallel design for very long half-life substances or the replicate design for substances with highly variable disposition. Single-dose studies generally suffice. However situations as described below may demand a steady-state study design:

i. Dose or time-dependant pharmacokinetics.
ii. Some modified release products (in addition to single dose investigations)
iii. Where problems of sensitivity preclude sufficiently precise plasma concentration measurements after single-dose administration.

iv. If intra-individual variability in the plasma concentration or disposition precludes the possibility of demonstrating bioequivalence in a reasonably sized single-dose study and this variability is reduced at steady state.

4.1.2. Study Population:

1. Selection of the Number of Subjects

The number of subjects required for a study should be statistically significant and is determined by the following considerations:

i. The error variance associated with the primary characteristic to be studied as estimated from a pilot experiment, from previous studies or from published data.
ii. The significance level desired: usually 0.05
iii. The expected deviation from the reference product compatible with bioequivalence.
iv. The required (discriminatory) power, normally ↕ 80% to detect the maximum allowable difference (usually± 20%) in primary characteristics to be studied.

The number of subjects recruited should be sufficient to allow for possible withdrawals or removals (dropouts) from the study. It is acceptable to replace a subject withdrawn/drop out from the study once it has begun provided the substitute follows the same protocol originally intended for the withdrawn subject and he/she is tested under similar environmental and other controlled conditions.

However, the minimum number of subjects should not be less than 16 unless justified for ethical reasons. In some cases 18-24 subjects may be needed.

Sequential or add-on studies are acceptable in specific cases e.g. where a large number of subjects are required or where the results of the study do not convey adequate statistical significance. In all cases the final statistical analysis must include data of all subjects or reasons for not including partial data as well as the un-included data must be documented in the final report.

2. Selection Criteria for Subjects:

To minimize intra and inter individual variation subjects should be standardised as much as possible and acceptable. The studies should be normally performed on healthy adult volunteers with the aim to minimise variability and permit detection of differences between the study drugs. Subjects may be males or females; however the choice of gender should be consistent with usage and safety criteria.

Risks to women of childbearing potential should be considered on an individual basis. Women should be required to give assurance that they are neither pregnant, nor likely to become pregnant until after the study. This should be confirmed by a pregnancy test immediately prior to the first and last dose of the study. Women taking contraceptive drugs should normally not be included in the studies.

They should normally be in the age range of 18-55 years.

If the drug product is to be used predominantly in the elderly attempts should be made to include as many subjects of 60 years of age or older as possible. If the drug product is intended for use in both sexes attempts should be made to include similar proportions of males and females in the studies.
For a drug representing a potential hazard in one group of users, the choice of subjects may be narrowed, e.g., studies on teratogenic drugs should be conducted only on males.

For drugs primarily intended for use in only males or only females — volunteers of only the respective gender should be included in the studies.

For drugs where the risk of toxicity or side effects is significant, studies may have to be carried out in patients with the concerned disease, but whose disease state is stable.

These should be screened for suitability by means of a comprehensive medical examination including clinical laboratory tests, an extensive review of medical history including medication history, use of oral contraceptives, alcohol intake, and smoking, use of drugs.
.
Depending on the study drug's therapeutic class and safety profile, special medical investigations may need to be carried out before, during and after the study.
3. Genetic Phenotyping
Phenotyping and/or genotyping of subjects should be considered for exploratory bioavailability studies and all studies using parallel group design. It may also be considered in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies etc.) for safety or pharmacokinetic reasons. If a drug is known to be subject to major genetic polymorphism, studies could be performed in panels of subjects of known phenotype or genotype for the polymorphism in question. While designing a study protocol, adequate care should be taken to consider Pharmacogenomic issues in the context of Indian population.

4.1.3. Study Conditions

Standardisation of the study environment, diet, fluid intake, post-dosing postures, exercise, sampling schedules etc. is important in all studies. Compliance with these standardisations should be stated in the protocol and reported at the end of the study, in order to reassure that all variability factors involved, except that of the products being tested, have been minimised. Unless the study design requires it, subjects should abstain from smoking, drinking alcohol, coffee, tea, xanthine containing foods and beverages and fruit juices during the study and for at least 48 hours before its commencement.

1. Selection of Blood Sampling Points/Schedules:

The blood-sampling period in single-dose trials of an immediate release product should extend to at least three-elimination half-lives. Sampling should be continued for a sufficient period to ensure that the area extrapolated from the time of the last measured concentration to infinite time is only a small percentage (normally less than 20%) of the total AUC. The use of a truncated AUC is undesirable except in certain circumstances such as in the presence of enterohepatic recycling where the terminal elimination rate constant cannot be calculated accurately.

There should be at least three sampling points during the absorption phase, three to four at the projected Tmax, and four points during the elimination phase. The number of points used to calculate the terminal elimination rate constant should be preferably determined by eye from a semi-logarithmic plot. Intervals between successive data/sampling points used to calculate the terminal elimination rate constant should, in general, not be longer than the half-life of the study drug.

Where urinary excretion is measured in a single-dose study it is necessary to collect urine for seven or more half-lives.

2. Fasting and Fed State Considerations:

Generally, a single dose study should be conducted after an overnight fast (at least 10 hours), with subsequent fast of 4 hours following dosing. For multiple dose fasting state studies, when an evening dose must be given, two hours of fasting before and after the dose is considered acceptable.

However, when it is recommended that the study drug be given with food (as it would in routine clinical practice), or where the dosage form is a modified release product, fed state studies need to be carried out in addition to the fasting state studies.

Fed state studies are also required when fasting state studies make assessment of Cmax and Tmax difficult.

Studies in the fed state require the consumption of a high-fat breakfast before dosing. Such a breakfast must be designed to provide 950 to 1000 KCals. At least 50% of these calories must come from fat, 15 to 20% from proteins and the rest from carbohydrates.

3. Steady State Studies:

In following cases — an additional “steady state study” is considered appropriate:

i. Where the drug has a long terminal elimination half-life and blood concentrations after a single dose cannot be followed for a sufficient time.

ii. Where assay sensitivity is inadequate to follow the terminal elimination phase for an adequate period of time.
iii. For drugs, which are so toxic that ethically they should only be administered to patients for whom they are a necessary part of therapy, but where multiple dose therapy is required, e.g. many cytotoxics.
iv. For modified-release products where it is necessary to assess the fluctuation in plasma concentration over a dosage interval at steady state.
v. For those drugs which induce their own metabolism or show large intraindividual variability.
vi. For enteric-coated preparations where the coating is innovative.
vii. For combination products where the ratio of plasma concentration of the individual drugs is important.
viii. For drugs that exhibit non-linear (i.e., dose- or time- dependent) pharmacokinetics.
ix. Where the drug is likely to accumulate in the body.

In steady state studies, the dosing schedule should follow the clinically recommended dosage regimen.

4.1.4. Characteristics to be investigated during bioavailability /bioequivalence studies

In most cases evaluations of bioavailability and bloequivalence will be based upon the measured concentrations of the active drug substance(s) in the biological matrix. In some situations, however, the measurements of an active or inactive metabolite may be necessary. These situations include (a) where the concentrations of the drug(s) may be too low to accurately measure in the biological matrix, (b) limitations of the analytical method, (c) unstable drug(s), (d) drug(s) with a very short half-life or (e) in the case of prodrugs.

Racemates should be measured using an achiral assay method. Measurement of individual enantiomers in bioequivalence studies is recommended where all of the following criteria are met:

(a) the enantiomers exhibit different pharmacodynamic characteristics
(b) the enantiomers exhibit different pharmacokinetic characteristics
(c) primary efficacy! safety activity resides with the minor enantiomer
(d) non-linear absorption is present for at least one of the enantiomers

The plasma-time concentration curve is mostly used to assess the rate and extent of absorption of the study drug. These include pharmacokinetic parameters such as the C_{max}, T_{max}, AUC_{0-t} and $AUC_{0-\infty}$

For studies in the steady state AUC_{0-T}, C_{max}, C_{min} and degree of fluctuation should be calculated.

4.1.5. Bioanalytical methodology:

The bioanalytical methods used to determine the drug and/or its metabolites in plasma, serum, blood or urine or any other suitable matrix must be well characterised, standardised, fully validated and documented to yield reliable results that can be satisfactorily interpreted.

Although there are various stages in the development and validation of an analytical procedure, the validation of the analytical method can be envisaged to consist of two distinct phases:

1. The pie-study phase which comes before the actual start of the study and involves the validation of the method on biological matrix human plasma samples and spiked plasma samples.
2. The study phase in which the validated bioanalytical method is applied to the actual analysis of samples from bioavailability and bioequivalence studies mainly to confirm the stability, accuracy and precision.

1. Pre-study Phase:
   The following characteristics of the bioanalytical method must be evaluated and documented to ensure the acceptability of the performance and reliability of analytical results:
   i. Stability of the drug!metabolites in the biological matrix:
      Stability of the drug and/or active metabolites in the biological matrix under the conditions of the experiment (including any period for which samples are stored before analyses) should be established. The stability data should also include the influence of at least three freezing and thawing cycles representative of actual sample handling. The absence of any sorption by the sampling containers and stoppers should also be established.
   ii. Specificity/selectivity:
      Data should be generated to demonstrate that the assay does not suffer from interference by endogenous compounds, degradation products, other drugs likely to be present in study samples, and metabolites of the drug(s) under study.
   iii. Sensitivity:
      Sensitivity is the capacity of the test procedure to record small variations in concentration. The analytical method chosen should be capable of assaying the drug/metabolites over the expected concentration range. A reliable lowest limit of quantification should be established based on an intra- and inter-day coefficient of variation usually not greater than 20 percent. The limit of detection (the lowest concentration that can be differentiated from background levels) is usually lower than the limit of quantification. Values between limit of quantification and limit of detection should be identified as “Below Quantification Limits.”
   iv. Precision and Accuracy:
      Precision (the degree of reproducibility of individual assays) should be established by replicate assays on standards, preferably at several concentrations. Accuracy is the degree to which the ‘true’ value of the

concentration of drug is estimated by the assay. Precision and accuracy should normally be documented at three concentrations (low, medium, high) where 'low' is in the vicinity of the lowest concentration to be measured, 'high' is a value in the vicinity of Cmax and 'medium' is a suitable intermediate value.

Intra-assay precision (within days) in terms of coefficient of variation should be no more than 15%, although no more than 20% may be more realistic at values near the lower limit of quantification. Inter-assay precision (between days) may be higher than 15% but not more than 20%.

Accuracy can be assessed in conjunction with precision and is a measure of the extent to which measured concentrations deviate from true or nominal concentrations of analytical standards. In general, an accuracy of ±15% should be attained.

v. Recovery:
Documentation of extraction recovery at high, medium and low concentrations is essential since methods with low recovery are, in general, more prone to inconsistency. If recovery is low, alternative methods should be investigated. Recovery of any internal standard used should also be assessed.

vi. Range and linearity:
The quantitative relationship between concentration and response should be adequately characterized over the entire range of expected sample concentrations. For linear relationships, a standard curve should be defined by at least five concentrations. If the concentration response function is non-linear, additional points would be necessary to define the non-linear portions of the curve. Extrapolation beyond the standard curve is not acceptable.

vii. Analytical System Stability:
To ensure that the analytical system remains stable over the time course of the assay, the reproducibility of the standard curve should be monitored during the assay. A minimal design would be to run analytical standards at the beginning and at the end of the analytical run.

2. Study Phase:
In general, with acceptable variability as defined by validation data, the analysis of biological sample can be done by single determination without a need for a duplicate or replicate analysis. The need for duplicate analysis should be assessed on a case-by-case basis. A procedure should be developed that documents the reason for re-analysis.

A standard curve should be generated for each analytical run for each analyte and should be used to calculate the concentration of the analyte in the unknown samples assayed with that run. It is important to use a standard

curve that will cover the entire range of concentrations in the unknown samples. Estimation of unknowns by extrapolations of standard curves below the lowest standard concentration or above the highest standard concentration is not recommended. Instead, it is suggested that standard curve should be redetermined or sample should be re-assayed after dilution. Quality control sample should be used to accept or reject the run.

3. Quality Control Samples:
   Quality control samples are samples with known concentration prepared by spiking drug-free biological fluid with drug. These samples should be prepared in low, medium and high concentration. To avoid possible confusion between quality control samples and standard solutions during the review process, preparation of quality control samples at concentrations different from those used for the calibration is recommended. For stable analytes, quality control samples should be prepared in the fluid of interest at the time of pre-study assay validation or at the time of study sample collection, and stored with the study samples. For less stable analytes, daily or weekly quality control samples may have to be prepared.

   A quality control sample for each concentration should be assayed on each occasion that study samples are assayed, and the concentration determined by reference to that day's calibration standards. If the concentration values determined for the controls are not within ±15% of the expected concentrations, the batch should be considered for re-analysis.

4. Repeat Analysis:
   In most studies some samples will require re-analysis because of aberrant results due to processing errors, equipment failure or poor chromatography. The reasons for re-analysis of such samples should be stated. The criteria for repeat analyses should be determined prior to running the study and recorded in the protocol I laboratory standard operating procedures.

4.1.6. Statistical Evaluation:

1. Data analysis:
   The primary concern in bio-equivalence assessment is to limit the consumer's risk i.e., erroneously accepting bioequivalence and also at the same time minimizing the manufacture's risk i.e., erroneously rejecting bioequivalence. This is done by using appropriate statistical methods for data analysis and adequate sample size.

2. Statistical analysis:
   The statistical procedure should be specified in the protocol itself. In case of bioequivalence studies the procedures should lead to a decision scheme which is symmetrical with respect to the two formulations (i.e. leading to the

same decision whether the new formulation is compared to the reference product or the reference product to the new formulation).

The statistical analysis (e.g. ANOVA) should take into account sources of variation that can be reasonably assumed to have an effect on the response.

The 90% confidence interval for the ratio of the population means (Test/reference) or two one sided-t tests with the null hypothesis of nonbioequivalence at the 5% significance level for the parameter under consideration are considered for testing bioequivalence.

To meet the assumption of normality of data underlying the statistical analysis, the logarithmic transformation should be carried out for the pharmacokinetic parameters Cmax and AUC before performing statistical analysis. However, it is recommended not to verify the assumptions underlying the statistical analysis before making logarithmic transformation. The analysis of Tmax is desirable if it is clinically relevant. The parameter Tmax should be analysed using non-parametric methods. In addition to above, summary statistics such as minimum, maximum and ratio should be given.

3. Criteria for bioequivalence:
   To establish Bioequivalence, the calculated 90% confidence interval for AUC and Cmax should fall within the bioequivalence range, usually 80-125%. This is equivalent to the rejection of two one sided-t tests with the null hypothesis of nonbioequivalence at 5% level of significance. The non-parametric 90% confidence interval for Tmax should lie within a clinically acceptable range.

   Tighter limits for permissible differences in bioavailability may be required for drugs that have:
   i. A narrow therapeutic index.
   ii. A serious, dose-related toxicity.
   iii. A steep dose/effect curve, or
   iv. A non-linear pharmacokinetics within the therapeutic dose range.

   A wider acceptance range may be acceptable if it is based on sound clinical justification.

   In case of supra-bioavailability, a reformulation followed by a fresh bioequivalence study will be necessary. Otherwise, clinical trial data on new formulation will be required to support the application, especially dosage recommendations. Such formulations are usually not be accepted as therapeutically equivalent to the existing reference product. The name of the new product should preclude confusion with the earlier approved product.

4. Deviations from the study plan:

The method of analysis should be defined in the protocol. The protocol should specify methods for handling drop-outs and for identifying biologically implausible outliers. Post hoc exclusion of outliers is not recommended. A scientific explanation should be provided to justify the exclusion of a volunteer from the analysis.

4.1. Special considerations for modified-release drug products:

For the purpose of these guidelines modified release products include:

i. Delayed release.
ii. Sustained release.
iii. Mixed immediate and sustained release.
iv. Mixed delayed and sustained release.
v. Mixed immediate and delayed release

Generally, these products should:

i. Act as modified-release formulations and meet the label claim.
ii. Preclude the possibility of any dose dumping effect.
iii. There must be a significant difference between the performance of modified release product and the conventional release product when used as reference product.
iv. Provide a therapeutic performance comparable to the reference immediate- release formulation administered by the same route in multiple doses (of an equivalent daily amount) or to the reference modified-release formulation;
v. Produce consistent pharmacokinetic performance between individual dosage units; and.
vi. Produce plasma levels which lie within the therapeutic range (where appropriate) for the proposed dosing intervals at steady state.

If all of the above conditions are not met but the applicant considers the formulation to be acceptable, justification to this effect should be provided.

i. Study Parameters:

Bioavailability data should be obtained for all modified release drug products although the type of studies required and the pharmacokinetic parameters which should be evaluated may differ depending on the active ingredient involved. Factors to be considered include whether or not the formulation represents the first market entry of the drug substance, and the extent of accumulation of the drug after repeated dosing.

If the formulation is the first market entry of the drug substance, the product's pharmacokinetic parameters should be determined. If the formulation is a second or subsequent market entry then comparative bioavailability studies using an appropriate reference product should be performed.

ii. Study design:

Study design will be single dose or single and multiple dose based on the modified release products that are likely to accumulate or unlikely to accumulate both in the fasted and non-fasting state. If the effect of food on the reference product is not known (or it is known that food affects its absorption), two separate two-way cross-over studies, one in the fasted state and the other in the fed state, may be carried out. If it is known with certainty (e.g. from published data) that the reference product is not affected by food, then a three-way cross-over study may be appropriate with:

a. the reference product in the fasting state
b. the test product in the fasted state, and
c. the test product in the fed state.

iii. Requirements for modified release formulations unlikely to accumulate:
This section outlines the requirements for modified release formulations which are used at a dose interval that is not likely to lead to accumulation in the body (AUC_{0-T} /$AUC0_{-\infty} \geq 0.8$).

When the modified release product is the first market entry of that type of dosage form, the reference product should normally be the innovator's immediate- release formulation. The comparison should be between a single dose of the modified release formulation and doses of the immediate-release formulation which it is intended to replace. The latter must be administered according to the established dosing regimen.

When the modified release product is the second or subsequent entry on the market, comparison should be with the reference modified release product for which bioequivalence is claimed.

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal at a specified time.
The following pharmacokinetic parameters should be calculated from plasma (or relevant biological matrix) concentrations of the drug and/or major metabolite(s): AUC_{0-T}, AUC_{0-t}, $AUC_{0-\infty}$, C_{max} (where the comparison is with an existing modified release product), and kel.

The 90% confidence interval calculated using log transformed data for the ratios (Test:Reference) of the geometric mean AUC (for both AUC_{0-T} and AUC_{0-t}) and C_{max} (where the comparison is with an existing modified release product) should generally be within the range 80 to 125% both in the fasting state and following the administration of an appropriate meal at a specified time before taking the drug.

The pharmacokinetic parameters should support the claimed dose delivery attributes of the modified-release dosage form.

iv. Requirements for modified release formulations likely to accumulate:

This section outlines the requirements for modified release formulations that are used at dose intervals that are likely to lead to accumulation (AUC_{0-T} /$AUC_{0-\infty} \geq 0.8$).
When a modified release product is the first market entry of the modified release type, the reference formulation is normally the innovator's immediate-release formulation. Both a single dose and steady state doses of the modified release formulation should be compared with doses of the immediate-release formulation which it is intended to replace. The immediate-release product should be administered according to the conventional dosing regimen.

Studies should be performed with single dose administration in the fasting state as well as following an appropriate meal. In addition, studies are required at steady state. The following pharmacokinetic parameters should be calculated from single dose studies: AUC_{0-T}, AUC_{0-t}, $AUC_{0-\infty}$, C_{max}). (where the comparison is with an existing modified release product), and k_{el}. The following parameters should be calculated from steady state studies: $AUC_{0-T(ss)}$, C_{max}, C_{min}, C_{pd} and degree of fluctuation.

When the modified release product is the second or subsequent modified release entry, single dose and steady state comparisons should normally be made with the reference modified release product for which bioequivalence is claimed.

The 90% confidence interval for the ratio of geometric means (Test:Reference drug) of AUC (for both AUC_{0-T} and AUC_{0-t}) and C_{max} (where the comparison is with an existing modified release product) determined using log-transformed data should generally be within the range 80 to 125% when the products are compared after single dose administration in both the fasting state and the fed state.

The 90% confidence interval for the ratio of geometric means (Test:Reference drug) for $AUC_{0-T(ss)}$, C_{max} and C_{min}, Cmn determined using log-transformed data should generally be within the range 80 to 125% when the formulations are compared at steady state.

The pharmacokinetic parameters should support the claimed attributes of the modified-release dosage form.

Pharmacodynamic data may reinforce or clarify interpretation of differences in the plasma concentration data.

Where these studies do not show bioequivalence, comparative efficacy and safety data may be required for the new product.

4.2. Pharmacodynamic Studies:
Studies in healthy volunteers or patients using pharmacodynamic parameters

may be used for establishing equivalence between two pharmaceutical products. These studies may become necessary if quantitative analysis of the drug and/or metabolite(s) in plasma or urine cannot be made with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic studies in humans are required if measurements of drug concentrations cannot be used as surrogate endpoints for the demonstration of efficacy and safety of the particular pharmaceutical product e.g., for topical products without an intended absorption of the drug into the systemic circulation.

In case, only pharmacodynamic data is collected and provided, the applicant should outline what other methods were tried and why they were found unsuitable.

i. The following requirements should be recognised when planning, conducting and assessing the results from a pharmacodynamic study:
ii. The response measured should be a pharmacological or therapeutic effect which is relevant to the claims of efficacy and/or safety of the drug.
iii. The methodology adopted for carrying out the study should be validated for precision, accuracy, reproducibility and specificity.
iv. Neither the test nor the reference product should produce a maximal response in the course of the study, since it may be impossible to distinguish differences between formulations given in doses that produce such maximal responses. Investigation of dose-response relationship may become necessary.
v. The response should be measured quantitatively under double-blind conditions and be recorded in a instrument-produced or instrument-recorded fashion on a repetitive basis to provide a record of pharmacodynamic events which are a substitute for plasma concentrations.
vi. If such measurements are not possible, recordings on visual-analogue scales may be used. In instances, where data are limited to qualitative (categorized) measurements, appropriate special statistical analyses will be required.
vii. Non-responders should be excluded from the study by prior screening. The criteria by which responders versus non-responders are identified must be stated in the protocol.
viii. Where an important placebo effect can occur, comparison between products can only be made by a priori consideration of the placebo effect in the study design. This may be achieved by adding a third period/phase with placebo treatment, in the design of the study.
ix. A crossover or parallel study design should be used, as appropriate.
x. When pharmacodynamic studies are to be carried out on patients, the underlying pathology and natural history of the condition should be considered in the study design. There should be knowledge of the reproducibility of the base-line conditions.
xi. In studies where continuous variables could be recorded, the time course of the intensity of the drug action can be described in the same way as in a study where plasma concentrations are measured. From this, parameters

can be derived which describe the area under the effect-time curve, the maximum response and the time when the maximum response occurred.

xii. Statistical considerations for the assessments of the outcomes are in principle, the same as in pharmacokinetic studies.

xiii. A correction for the potential non-linearity of the relationship between dose and area under the effect-time curve should be made on the basis of the outcome of the dose ranging study.

The conventional acceptance range as applicable to pharmacokinetic studies and bioequivalence is not appropriate (too large) in most cases. This range should therefore be defined in the protocol on a case-to-case basis.

4.3. Comparative Clinical Studies:

In several instances (For example, section 3.1.1(e) above), the plasma concentration time-profile data may not be suitable to assess equivalence between two formulations. Whereas in some of the cases pharmacodynamic studies can be an appropriate tool for establishing equivalence, in other instances this type of study cannot be performed because of lack of meaningful pharmacodynamic parameters which can be measured and a comparative clinical study has to be performed in order to demonstrate equivalence between two formulations. Comparative clinical studies may also be required to be carried out for certain orally administered drug products when pharmacokinetic and pharmacodynamic studies are not feasible. However, in such cases, the applicant should outline what other methods were tried and why they were found unsuitable.

If a clinical study is considered as being undertaken to prove equivalence, the appropriate statistical principles should be applied to demonstrate bioequivalence. The number of patients to be included in the study will depend on the variability of the target parameters and the acceptance range, and is usually much higher than the number of subjects in bioequivalence studies.

The following items are important and need to be defined in the protocol in advance:

a. The target parameters which usually represent relevant clinical end-points from which the intensity and the onset, if applicable and relevant, of the response are to be derived.
b. The size of the acceptance range has to be defined case-to- case taking into consideration the specific clinical conditions. These include, among others, the natural course of the disease, the efficacy of available treatments and the chosen target parameter. In contrast to bioequivalence studies (where a conventional acceptance range is applied) the size of the acceptance range in clinical trials cannot be based on a general consensus on all the therapeutic classes and indications.

c. The presently used statistical method is the confidence interval approach. The main concern is to rule out that the test product is inferior to the reference product by more than the specified amount. Hence, a one-sided confidence interval (for efficacy and/or safety) may be appropriate. The confidence intervals can be derived from either parametric or nonparametric methods.
d. Where appropriate, a placebo leg should be included in the design.
e. In some cases, it is relevant to include safety end-points in the final comparative assessments.

4.4. In Vitro studies

In certain situations a comparative in vitro dissolution study may be sufficient to demonstrate equivalence between two drug products (See Section 3).

The test methodology adopted should be in line with the pharmacopoeial requirements unless those requirements are shown to be unsatisfactory. Alternative methods may be acceptable provided they have sufficient discriminatory power.

Dissolution studies should generally be carried out under mild agitation conditions at 37±0.5°C and at physiologically relevant pH. More than one batch of each formulation should be tested. Comparative dissolution profiles, rather than single point dissolution test data, should be generated. The design should include:

ii. Individually testing of at least twelve dosage units (e.g., tablets, capsules) of each batch. Mean and individual results should be reported along with their standard deviations or standard errors.
iii. Measuring the percentage of nominal content released at a number of suitably spaced time points to provide a profile for each batch, e.g. at 10, 20 and 30 minutes or as appropriate to achieve virtually complete dissolution.
iv. Determining the dissolution profile in at least three aqueous media covering the pH range of 1.0 to 6.8 or in cases where considered necessary, pH range of 1.0 to 8.0.
v. Conducting the tests on each batch using the same apparatus and, if possible, on the same or consecutive days.

Comparisons of the dissolution profiles may be made by any of the established model-independent or model-dependent methods.

5. DOCUMENTATION:

With respect to the conduct of bioequivalence/bioavailability studies following important documents must be maintained:

i. Clinical Data:
   a. All relevant documents as required to be maintained for compliance with GCP Guidelines.

ii. Details of the analytical method validation including the following:
   a. System suitability test
   b. Linearity range
   c. Lowest limit of quantitation
   d. QC sample analysis
   e. Stability sample analysis
   f. Recovery experiment result

iii. Analytical data of volunteer plasma samples which should include the following:
   a. Validation data of analytical methods used
   b. Chromatograms of all volunteers, including any aberrant chromatograms
   c. Inter-day and intra-day variation of assay results
   d. Details including chromatograms of any repeat analysis performed
   e. Calibration status of the instruments

iv. Raw data

v. All comments of the chief investigator regarding the data of the study submitted for review.

vi. A copy of the final report

6. STUDY REPORT

The bioequivalence or bioavailability report should give the complete documentation of its protocol, conduct and evaluation.

The report should include (as a minimum) the following information:

   a. Table of contents
   b. Title of the study
   c. Names and credentials of responsible investigators
   d. Signatures of the principal and other responsible investigators, authenticating their respective sections of the report
   e. Site of the study and facilities used
   f. The period of dates over which the clinical and analytical steps were conducted
   g. Names and batch numbers of the products compared
   h. A signed declaration that this was identical to that intended for marketing.
   i. Results of assays and other pharmaceutical tests (e.g., physical description, dimensions, mean weight, weight uniformity, comparative dissolution) carried out on the batches of products compared
   j. Full protocol for the study criteria for inclusion/exclusion or withdrawal of subjects
   k. Report of protocol deviations, violations

l. Documentary evidence that the study was approved by an independent ethics committee and was carried out in accordance with GCPJGLP
m. Demographic data of subjects
n. Names and addresses of subjects
o. Details of and justifications for protocol deviations
p. Details of dropout and withdrawals from the study should be fully documented and accounted for
q. Details of analytical methods used, full validation data, quality control data and criteria for accepting or rejecting assay results
r. Representative chromatograms covering the whole concentration range for all, standard and quality control samples as well as specimens analysed
s. Sampling schedules and deviations of the actual times from the scheduled
t. Details of how pharmacokinetic parameters were calculated
u. Documentation related to statistical analysis:
   i. Randomization schedule
   ii. Volunteer wise plasma concentration and time points for test and reference products
   iii. Volunteer wise AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $C_{max,}$ K_{el} and $t_{1/2}$ for test and reference products
   iv. Logarithmic transformed measures used for BE demonstration
   v. ANOVA for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}
   vi. Inter-subject, intra-subject and/or total variability if possible
   vii. Confidence intervals for AUC_{0-t}, $AUC_{0-\infty}$, C_{max} (Confidence interval (Cl) values should not be rounded off; therefore, to pass a Cl range of 80 to 125, the values should be at least 80.00 and not more than 125.00
   viii. Geometric mean, arithmetic mean, ratio of means for AUC_{0-t}, $AUC_{0-\infty}$, C_{max}
   ix. Partial AUC, only if it is used
   x. C_{min}, C_{max}, C_{pd}, AUC_{0-T}, degree of fluctuation $[(C_{max} - C_{min})/C_{av}]$ and swing $[(C_{max} — C_{min})/C_{min}]$, if steady state studies are employed

7. FACILITIES FOR CONDUCTING BIOAVALABILITY AND/OR BIOEQUIVALENCE STUDIES

Legal identity:

The organization, conducting the bioequivalence ***I*** bioavailability studies, must be a legally constituted body with appropriate statutory registrations.

Impartiality, confidentiality, independence and integrity**:**

The organization shall:

a. have managerial staff with the authority and the resources needed to discharge their duties.
b. have arrangements to ensure that its personnel are free from any commercial, financial and other pressures which might adversely affect the quality of their work.

c. be organized in such a way that confidence in its independence of judgment and integrity is maintained at all times.
d. have documented policies and procedures, where relevant, to ensure the protection of its sponsors' confidential information and proprietary rights.
e. not engage in any activity that may jeopardize the trust in its independence of judgement and integrity
f. have documented policies and procedures for the safety of human rights and the use of human subjects in research consistent with Schedule Y
g. have documented policies and procedures for scientific integrity including procedures dealing with and reporting possible scientific misconduct.

Organisation and management**:**
The study site organization must include the following:

a. An Investigator who has the overall responsibility to provide of the human subjects. The Investigator(s) should possess appropriate medical qualifications and relevant experience for conducting pharmacokinetic studies.
b. The site should have identified adequately qualified and trained personnel to perform the following functions:
   i. Clinical Pharmacological Unit (CPU) management
   ii. Analytical laboratory management
   iii. Data handling and interpretation
   iv. Documentation and report preparation
   v. Quality assurance of all operations in the centre

Documented Standard Operating Procedures:
The centre shall establish and maintain a quality system appropriate to the type, range and volume of its activities. All operations at the site must be conducted as per the authorized and documented standard operating procedures. These documented procedures should be available to the respective personnel for ready reference. The procedures covered must include those that ensure compliance with all aspects of:

a. GCP Guidelines
b. Good laboratory practice guidelines.

A partial list of procedures for which documented standard operating procedures should be available includes:

b. maintenance of working standards (pure substances) and respective documentation.
c. withdrawal, storage and handling of biological samples.
d. maintenance, calibration and validation of instruments.
e. managing medical as well as non-medical emergency situations
f. handling of biological fluids
g. t managing laboratory hazards

h. disposal procedures for clinical samples and laboratory wastes
i. documentation of clinical pharmacology unit observations, volunteer data and analytical data
j. obtaining informed consent from volunteers
k. volunteer screening and recruitment and management of ineligible volunteers
l. volunteer recycling (using the same volunteer for more than one study
m. randomization code management
n. study subject management at the site (including check-in and check-out procedures)
o. recording and reporting protocol deviations
p. recording, reporting and managing scientific misconduct
q. monitoring and quality assurance

Wherever possible, disposable (sterile, wherever applicable) medical devices must be used for making subject interventions.

Clinical Pharmacological Unit
It must have adequate space and facilities to house at least 16 volunteers. Adequate area must be provided for dining and recreation of volunteers, separate from their sleeping area.

Additional space and facilities should also be provided for the following:
a. Office and administrative functions
b. Sample collection and storage
c. Control sample storage
d. Wet chemical laboratory
e. Instrumental Laboratory
f. Library
g. Documentation archival room
h. Facility for washing, cleaning and Toilets
i. Microbiological laboratory (Optional)
j. Radio Immuno — Assay room (optional)

8. MAINTENANCE OF RECORDS OF BAIBE STUDIES
All records of in vivo or in vitro tests conducted on any marketed batch of a drug product to assure that the product meets a bioequivalence requirement shall be maintained by the Sponsor for at least 2 years after the expiration date of the batch and submitted to CDSCO on request.

9. RETENTION OF BA/BE SAMPLES
All samples of test and reference drug products used in bioavailability / bioequivalence study should be retained by the organization carrying out the

bioavailability/ bioequivalence study for a period of three years after the conduct of the study or one year after the expiry of the drug, whichever is earlier. The study sponsor and/or drug manufacturer should provide to the testing facility batches of the test and reference drug products in such a manner that the reserve samples can be selected randomly. This is to ensure that the samples are in fact representative of the batches provided by the study sponsor and/or drug manufacturer and that they are retained in their original containers. Each reserve sample should be of sufficient quantity sufficient to twice carry out all the invitro and in-vivo tests required during bioavailability / bioequivalence study.

The reserve sample should be stored under conditions consistent with product labelling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel.

10. SPECIAL TOPICS:

10.1 Food effect bioavailability studies

Food effect study is required when there is a possibility that food have an effect on the bioavailability of the drug. Food effect bioavailability studies focus on effects of food on the release of the drug substance from the drug product as well as the absorption of the drug substance. Usually, a single dose crossover study is recommended for BA and BE studies.

10.2 Long half-life drugs

For BE determination of an oral product with a long half life, a single dose crossover study can be conducted, provided an adequate wash out period is used. If due to longer periods, chances of drop outs as well as intra subject variation are higher with routine cross over designs; parallel group designs can be used. In all cases, blood sampling period should be adequate to describe the plasma concentration time profile. Cmax and a suitably truncated AUC can be used to characterize peak and total drug exposure, respectively. For drugs, demonstrating high intra-subject variability in distribution and clearance, AUC truncation warrants caution. In such cases, sponsors and/or applicants should consult the regulatory authority.

10.3 Early Exposure

In general, bioequivalence may be demonstrated by measurements of peak and total exposure for an immediate release product. However, in situations such as rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive, an early exposure measure may be informative on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic / pharmacodynamic studies that call for better control of drug absorption into the systemic circulation. In these situations, use of partial AUC is recommended as an early exposure measure. The partial area should be truncated at ‘max values for the reference formulation. At least two

quantifiable samples should be collected before the expected peak time to allow adequate estimation of the partial area.

Individual and population bioequivalence:
The current practice of evaluating bioequivalence has been termed as "average bioequivalence". Whereas in individual bioequivalence, determination of the intra subject variation of drug response is important. By "population bioequivalence" we mean a bioequivalence criterion that requires the distribution of the formulation to be sufficiently similar to that of the reference in some appropriate population. Average bioequivalence is a special case of population bioequivalence.
The average bioequivalence of the two formulations is important in the case of prescribability. However, individual bioequivalence is required in case of switchability.
Assessment of individual bioequivalence is an interesting and exciting alternative to the current practice of evaluating average bioequivalence. The evaluation of individual bioequivalence requires values of intra-subject variability of the test and reference formulations. Hence the assessment of individual bioequivalence is done based on three or four period designs. Replicate study designs provide such information. Up till now, bioequivalence studies are designed to evaluate average bioequivalence. Experience with population and individual bioequivalence studies is limited. Hence no specific recommendation is proposed on this matter. However, for highly variable drugs, individual bioequivalence can be considered.