

GUIDELINES on the REGISTRATION of PHARMACEUTICALS for HUMAN USE in UGANDA (Revised July 2006)

1. GENERAL

These guidelines apply to all pharmaceutical products other than biological products, traditional medicinal products, diagnostic aids, medical appliances and public health chemicals.

- 1.1 All documents are to be submitted typewritten or computer printed in ENGLISH. Where originals are in another language, copies shall be presented together with certified English translations.
- 1.2 Each complete application must contain a complete index to the various appendices and each page of the application dossier must be numbered.
- 1.3 The appropriate application fees shall accompany each complete application form. (See Annex I). Subsequent applications to amend any part of the application shall also be accompanied by appropriate fees per change. The guidelines on submission of amendment applications (Annex II) shall be followed.
- 1.4 Registration procedures shall commence only if Form NDA: R1 with its appendices has been properly completed. As and when the need arises, NDA may request for information not spelled out in these guidelines.
- 1.5 All documents shall be addressed to:

The Executive Secretary / Registrar,
National Drug Authority, Plot 46 –48 Lumumba Avenue
PO Box 23096, Kampala, UGANDA

Phone: (+256) 41-255665 / 347391/ 347392

Fax: (+256) 41-255758

E-mail: ndaug@nda.or.ug

- 1.6 Payment of fees can be made by Bank Transfer to:

National Drug Authority Account no: 0240060034201
Stanbic Bank Uganda Limited, Kampala or by bank draft in favour of
National Drug Authority

- 1.7 All pharmaceutical products are registrable and must therefore be registered in Uganda before sale and distribution.

2. APPLICANT

- 2.1 Application for the registration of a drug shall be made only by:
 - the license/patent holder
 - the manufacturer
 - a distributor authorised by the manufacturer, license/patent holder
 - an authorised Local Technical Representative (LTR) of the manufacturer or license/patent holder (see section 5 below)

The name, physical address, telephone number, fax number, and e-mail address of the applicant shall be provided.

1. PARTICULARS OF THE PRODUCT

- 3.1 **Proprietary name** means the (trade or brand) name which is unique to a particular drug and by which it is generally identified (and by which it is registered in the country of manufacture).
- 3.2 **Approved / INN / generic name** in relation to a drug means the internationally recognised non-proprietary name of such a drug or such other name as the NDA may determine.
- 3.3 **Strength** shall be given per unit dosage form or per specified quantity: eg. mg per tablet, mg per capsule, mg/mL, mg per 5mL spoonful, mg per G, etc.
- 3.4 **Pharmaceutical form** shall mean the form in which the drug is presented, eg. solution, suspension, eye drops, emulsion, ointment, suppository, tablet, capsule, etc. For injections, the type of presentation (eg. vial, ampoule, dental cartridge, etc), and the type of content (eg. powder for reconstitution, solution, suspension, oily solution, etc.) shall also be stated.
- 3.5 **Description of the drug** shall mean a full visual description of the drug including colour, size, shape and other relevant features, eg. 'black and red gelatin capsule with marks "Amp -250", 'pink film-coated tablets with word "PAN" embossed on one side' etc.
- 3.6 **Labelling:** The applicant shall ensure that the primary (immediate) packaging of the product is labelled according to the law applicable in Uganda. The following minimum information shall be required in English on the label of the immediate packaging:
- i) brand name where appropriate
 - ii) International non-proprietary name/generic name
 - iii) Pharmaceutical form, quantity of active ingredient per dosage unit
 - iv) total contents of container
 - v) date of manufacture
 - vi) date of expiry
 - vii) batch number
 - viii) specific storage conditions (see section 8.5)
 - ix) name and full location address of manufacturer

Any drug product whose name, package or label bears close resemblance to an already registered product, or is likely to be mistaken for such a registered product, shall not be considered for registration. Disputes regarding trademark infringements not identified by NDA at the time of registration or amendment shall be the responsibility of the applicants. If however, valid safety concerns are identified, the new applicant shall be advised to make appropriate amendments.

Due to lack of space, the date of manufacture, address of the manufacturer and storage conditions may be omitted on the primary container if it is a blister or strip pack, or a vial or an ampoule less than 10mL.

The name of the manufacturer may be substituted with a trade-mark or other symbol. However these details shall appear in full on the secondary packaging.

Labels shall not contain material written or graphical that targets to directly promote use of the products by infants and children. Pictograms intended to clarify certain information (e.g. age group for which product is intended, dosage e.t.c.) may be included on the product package.

All particulars on the label shall be easily legible, clearly comprehensible and indelible.

- 3.7 **Information leaflet:** The product packaging shall include a prescribing information leaflet in the case of prescription medicines, or a patient information leaflet in the case of non-prescription medicines. The leaflet shall include the following minimum information:
- i) International Non-proprietary Name (INN) for each active ingredient
 - ii) Pharmacology: a brief description of the mechanism of action and pharmacological effects
 - iii) Clinical Information:
 - a) indications
 - b) dosage regimens, including for children
 - c) contraindications
 - d) precautions in pregnancy, lactation, renal and hepatic failure etc
 - e) adverse reactions including their frequency
 - f) clinically significant drug interactions
 - g) symptoms and treatment of overdose
 - iv) Pharmaceutical Information:
 - a) dosage form
 - b) strength
 - c) excipients
 - d) storage conditions
 - e) shelf-life
 - f) pack size
 - g) description of product and package
 - h) name and address of the manufacturer

4. PARTICULARS OF THE MANUFACTURER(S) AND ACTIVITY

The name, physical address, telephone number, fax number, and e-mail address of the manufacturer shall be provided.

Where different activities of manufacture of a given product are carried out at different manufacturing sites, the above particulars shall be provided for each site and the activity carried out at the particular site shall be stated as in the examples below.

	Name	Address	Activity
1.	UgaPharma	Plot 4, City Rd, Kampala PO Box 5445, Kampala, Uganda Tel: 222207	Granulation
2.	T.M. Pharmaceuticals	Plot 73, Government Avenue, Nairobi PO Box 3459, Nairobi, Kenya Tel: 222218	Compression Coating
3.	Goodman Limited	GLN, 13LT, London, UK Tel: 235 898 491	Packing

A copy of a valid manufacturing licence shall be provided for each site. Only products entirely manufactured at sites that meet NDA's requirements for Good Manufacturing Practice shall be eligible for registration.

5. AUTHORISED REPRESENTATIVE IN UGANDA

In case the product is manufactured outside Uganda, a body corporate (company), licensed to handle pharmaceuticals, shall be the applicant's local representative in Uganda with legal authorisation to take full responsibility for the product on behalf of the patent/license holder or manufacturer, and will be answerable to NDA. This body corporate shall be called the **Local Technical Representative (LTR)**. A copy of the legal authority given to the representative or agent shall be enclosed. Such a body may be:

- a) a wholesale pharmacy
- b) a retail pharmacy
- c) a registered local branch/office of the applicant, in which a pharmacist is employed

6. SIGNATORY

The signatory shall be a pharmacist registered in Uganda working for and/or authorised by the manufacturer / applicant. The pharmacist's designation and qualification shall be stated.

7. APPENDIX 1 (of Form NDA: R1)

7.1 SPECIFICATIONS OF THE PACKAGING MATERIAL

The following information shall be provided:

- a) A general description of the container and closure system including primary (inner) and secondary (outer) packaging, and other components such as spoons and syringes.
- b) The chemical identity of materials for each component of the system
- c) Detailed specifications and tests for primary (immediate) packaging components such as:

- ▶ glass containers
- ▶ plastic containers and closures for solid dosage forms, ophthalmics, parenterals, blood products
- ▶ rubber closures

Such specifications and tests shall be as per the British Pharmacopoeia, European Pharmacopoeia, or United States Pharmacopoeia, or in-house, and certificates of analysis shall be provided as proof that the packaging conforms to specifications.

- ▶ Evidence of suitability of the container and closure system for the finished product:
 - compatibility of primary packaging components with finished product.
 - performance of system in drug delivery, e.g. actual volumes of teaspoons and eye drop bottles, extractable volumes of vials and ampoules.
 - protection from moisture and light

d) Special attention should be paid to the following product categories:

- ▶ Oral liquid products packed in multi-dose containers should be provided with suitable graduated measuring devices to facilitate correct dose administration. Powders meant for reconstitution before oral administration should additionally have their containers designed with a permanently engraved reconstitution mark.
- ▶ Ampoules should be made with break-lines or other suitable design for the purpose of facilitating opening while preventing product contamination.
- ▶ For hygroscopic products presented in bulk packs, data to support stability after date of first opening should be provided. The assigned shelf-life after first opening should also be declared on the pack.

7.2 COMPOSITION OF THE PRODUCT

The approved / INN /generic name(s) and the chemical name(s) of the substances (active and inactive) shall be given, and in the absence of a chemical name, the chemical nature of the substance shall be described. Trade names shall not be used.

Quantities shall be given in terms of the dosage unit, eg. mg/tablet, mg/mL, etc.

Specifications or reference text shall be precisely stated, eg. BP 93 page 101.

The reason for inclusion of each inactive ingredient in the formulation shall be stated. Any raw materials used, although not present in final dosage form, shall also be stated.

8. APPENDIX 2 (of Form NDA: R1)

8.1 Raw material specifications

- 1) Raw material specifications and details of their analytical methods shall be given. Where pharmacopoeial references to specifications and analytical methods are given, full photocopies of such references (monographs) should be supplied.
- 2) For non-pharmacopoeial active raw materials the following minimum information should be provided:
 - a) **Specifications and tests for all active raw materials:**
 - i) Description
 - ii) Identification: test method should be selective
 - iii) Assay: test method should be selective and able to detect degradation compounds ie. it should be stability-indicating.
 - iv) Impurity limits:
 - ▶ Organic impurities (generated during synthesis: starting materials, by-products like isomers and polymorphs, intermediates, degradation products, reagents, catalysts)
 - If $\geq 0.1\%$ of active ingredient content it should be characterised (identified) and evidence of its safety provided
 - If $< 0.1\%$, characterization is not necessary, and quantification only is required.
 - ▶ Inorganic impurities (used during synthesis- reagents, ligands, heavy metals and inorganic salts).
 - Limits should be pharmacopoeial
 - ▶ Residual solvents (used during synthesis)
 - In all cases where there are residual solvents, limits should be stated, and those limits justified.
 - v) Analytical method validation report for in-house methods (see Annex III)
 - b) **Additional specifications and tests for relevant active raw materials:**
 - i) Physicochemical properties (eg. melting point, pH in solution, refractive index)
 - ii) Solid-state form (polymorphs and solvates)
 - iii) Optical activity (to control enantiomeric purity)
 - iv) Water content (for hygroscopic or sensitive compounds)
 - v) Microbial limits (for susceptible compounds)
 - vi) Particle size, bulk density, flow
 - vii) Solubility in water and other solvents

All tests should be performed unless development pre-formulation studies or process validation proves them unnecessary. Such proof should be provided in the application dossier.

Copies of the supplier's or manufacturer's Certificates of Analysis shall be supplied for each raw material as proof of conformance to all declared specifications.

- 8.2 **Comprehensive details of the procedures involved in the various stages of manufacture**, including packaging shall be given. This shall be in the form of a detailed flow diagram accompanied by a list of equipment used at each stage.
- 8.3 **Analytical, microbiological and other in-process control procedures** together with the frequency and sequence in which they are carried out during the manufacturing process shall be stated. These processes shall be included in the flow diagram above.
- 8.4 **Specifications of the finished product** shall be given, ie. the acceptable limits of all the physical, chemical, biological and (where applicable) microbiological parameters. A full description of analytical and other control procedures carried out to ascertain the final

product specifications stated above shall be given.

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

For pharmacopoeial finished products, photocopies of the relevant monographs may be provided .

For pharmacopoeial finished products where the methods of analysis used are non-pharmacopoeial, detailed analytical validation of such methods shall be provided (see Annex III).

For non-pharmacopoeial (in-house) finished products the following minimum information shall be provided.

- 1) **Specifications and test methods (for all dosage forms)**
 - a) Description
 - b) Identity - test method should be specific for active ingredient(s)
 - c) Assay - test method should be specific and stability indicating for active ingredient(s)
 - d) Impurity limits - to determine the level of degradation products of active ingredients, and active ingredient-exciipient interaction impurities.
 - e) Analytical method validation report (see Annex III)
- 2) **Additional specifications and test methods for hard gelatin capsules and tablets**
 - a) Dissolution (for relatively water insoluble active ingredients)
 - b) Disintegration (for readily soluble active ingredients)
 - c) Dissolution profiles for modified release preparations
 - d) Hardness & friability
 - e) Uniformity of content and mass (dosage units)
 - f) Water content
 - g) Microbial limits
- 3) **Additional specifications and test methods for oral liquids**
 - a) pH
 - b) Microbial limits
 - c) Antimicrobial preservative content/ preservative efficacy test
 - d) Antioxidant preservative content
 - e) Extractables from primary container
 - f) Alcohol content
 - g) Dissolution of suspensions
 - h) Particle size distribution
 - i) Redispersibility
 - j) Specific gravity
 - k) Water content
- 4) **Additional specifications and test methods for parenterals**
 - a) Uniformity of content and mass
 - b) pH
 - c) Sterility
 - d) Endotoxins/pyrogens
 - e) Particulate matter
 - f) Water content

- g) Antimicrobial preservative content/PET
- h) Antioxidant preservative content
- i) Extractables
- j) Functionality of delivery systems, eg. syringeability for pre-filled syringes
- k) Osmolality
- l) Particle size distribution
- m) Redispersibility

All tests should be performed unless development pharmaceuticals studies or process validation prove that they are unnecessary. Such proof should be provided in the application dossier.

8.5 Stability

studies

Evidence of stability of the product shall be submitted as follows:

Stability studies on finished products:

- a) The products should be tested in the packaging intended for marketing
- b) The investigator should be identified and should sign the study report
- c) The date and location of the studies should be identified
- d) Type of study should be specified (accelerated, real time)
- e) A detailed protocol should be given
- f) Summarised results
- g) Conclusions on:
 - i) Proposed storage conditions
 - ii) Proposed shelf-life
 - iii) In-use storage conditions and shelf-life
- h) Post-approval stability studies commitment - in case shelf-life is not covered at the time of submission of the dossier.
- i) Studies for generic products in conventional dosage forms shall be conducted and documented in the following way (based on WHO recommendations):

Objective: The aim of the studies shall be to establish shelf-life and storage conditions appropriate to climatic zone IV.

Type of study: The applicant shall specify whether the studies are real time or accelerated.

Protocol:

- ▶ **Test samples** (from pilot or production batches)
 - 2 different batches for stable active ingredient
 - 3 different batches for unstable active ingredients (as defined by WHO classification)
 - Active ingredients should also be from different batches wherever possible
 - The selection of samples for testing from each batch should be random.
- ▶ **Storage conditions for real time studies**
 - 30°C ± 2°C, 65% ± 5% RH
 - Conditions must be controlled (ie. in stability chambers and not on open shelves)
 - Products intended for storage in a refrigerator: 5 °C± 3°C
 - Studies should last for at least 6 months by the time of dossier submission
 - Studies should continue to the end of the proposed shelf-life (a written commitment to this should be made by the applicant).

- ▶ **Storage conditions for accelerated studies**
 - 40 °C ± 2°C, 75% ± 5% RH
 - Products intended for storage in a refrigerator: 25°C ± 2°C, 65% ± 5% RH
 - Duration 6 months

- ▶ **Selection of samples for testing:** a description of the sampling plan used to select samples from the test batch, for storage and subsequent testing, shall be given.

- ▶ **Orientation of containers:** for liquid and semi-solid products, samples should be stored in upright, horizontal and inverted positions to ensure full interaction with all primary packaging materials.

- ▶ **Frequency of testing**
 - Accelerated study: 0, 1, 2, 3 and 6 months
 - Real-time study: 0, 6, 12 months, and thereafter annually

- ▶ **End-of-shelf-life specifications with limits** shall be stated

- ▶ **Analytical tests** (all test methods shall be fully described)
 - Appearance
 - Assay - stability indicating method shall be used
 - Content of decomposition products (impurities)
 - Physicochemical properties, eg. hardness, disintegration, particulate matter, pH
 - Dissolution for all solid or semi-solid oral dosage forms.
 - Preservative efficacy tests.

- ▶ **Analytical method validation** for non-pharmacopoeial assay methods shall be provided.

- ▶ **Products to be reconstituted before use:** tests on the stability of these after reconstitution should also be done and a shelf-life of the reconstituted product determined.

- ▶ **Multi-dose vials for liquid injectables:** tests should be done to determine stability after the first puncturing.

- ▶ **Drug products packaged in impermeable containers:** Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition. Containers that are generally considered to be moisture impermeable include: glass ampoules, Aluminium/Aluminium blisters and High Density Polyethylene (HDPE) or glass bottles fitted with HDPE or metal closures.

- ▶ **Drug products packaged in semi-permeable containers:** Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. Ultimately, it should be demonstrated that they can withstand low relative humidity environments. Reference shall be made to International Conference on Harmonization guidelines on stability testing of new drug substances and products.

- ▶ Where the product is to be registered in several strengths or pack sizes, bracketing or matrixing may be applied, as described in the relevant section of International Conference on Harmonization guidelines.

Presentation of results

- ▶ Should be both as tables and as graphs.

Interpretation of results and shelf-life determination

- ▶ Shall be based on the least stable batch 24 months shelf-life can be assigned if:
 - the active ingredient is known to be stable (WHO classification) ;
 - 6-month studies show no significant change (accelerated or real time) and applicant has given written commitment to continue the studies and provide results up to at least 24 months.
- if an active ingredient is known to be unstable, or accelerated studies are unsuitable for the formulation, eg. suppositories, the shelf-life assigned would be 2 times the period of real time studies so far conducted.
- A shelf-life of greater than 24 months can be granted as long as real time studies are conducted for at least as long as the proposed shelf-life and indicate stability of the product

Storage labelling recommendations

- ▶ Shall be stated as follows:
 - Store under normal storage conditions (15°C - 30°C)
 - Store between 2°C - 8°C (refrigeration, no freezing)
 - Store below 8°C (refrigeration)
 - Store between -5°C - 0°C (in a freezer)
 - Store below -18°C (in a deep freezer)

Note that these recommendations must be reflected on the product samples submitted with the application.

Retesting

- ▶ Stability studies should be repeated if there are changes in the formulation, manufacturing method, or packaging material of a product.

Note: For products with active ingredients which are new chemical entities, and for modified release products, the guidelines of the International Conference on Harmonization (ICH) shall be followed.

8.6 Batch Manufacturing Records (BMR)

Copies of original documents used in the manufacture of one complete batch, ie. from release of raw materials to release of final product for marketing, shall be submitted including QC reports.

Batch records for one particular batch should include:

- a) Raw material and packaging material requisition records
- b) Line clearance records
- c) Processing records
- d) Packaging records
- e) Reconciliation records
- f) Sterilisation records
- g) Certificates of Analysis of the finished product.
- h) All other records as required by WHO GMP guidelines

Exemption from provision of batch manufacturing records by applicants for research based innovator products may be granted on a case-by-case basis, upon application for such exemption.

9. APPENDIX 3 (of Form NDA: R1)

- 9.1 If the drug has been registered in the country of manufacture, the conditions of registration and copy of the registration certificate/marketing authorisation shall be submitted.
- 9.2 A copy of the manufacturing licence of the manufacturer shall be provided.
- 9.3 If a product is not registered in country of manufacture, a valid explanation must be given.
- 9.4 As an alternative to 9.1 and 9.2, a *Certificate of a Pharmaceutical Product* shall be submitted under the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, where the exporting country shall be the country of manufacture and importing (requesting country) shall be the Republic of Uganda.
- 9.5 For new chemical entities and new fixed dose combinations, the outcome of pre-marketing evaluation of safety and efficacy and post-marketing evaluation of safety by a well resourced national regulatory authority or WHO advice shall be required before marketing authorization may be considered.

10. APPENDIX 4 (of Form NDA: R1)

- 10.1 **Particulars of toxicological trials carried out**
Details of laboratory tests and their conclusions performed to demonstrate all aspects of toxicity of the drug, and to predict toxicity during use, shall be provided, with special reference to:
- ▶ Single dose toxicity
 - ▶ Repeat dose toxicity
 - ▶ Genotoxicity including mutagenicity
 - ▶ Carcinogenicity
 - ▶ Reproductive toxicity
 - Effects on fertility and early embryonic development
 - Effects on embryo-foetal development
 - Effects on prenatal and postnatal development
 - ▶ Local tolerance (potential for adverse effects at site of administration)
 - ▶ Potential for dependence and abuse
 - ▶ Environmental impact assessment for biotechnology products.
- 10.2 **Particulars of therapeutic effects and indications of a drug.**

The proposed therapeutic use(s) of the product shall be stated. Evidence of potential benefit of use in Uganda shall be provided. Such evidence may be found in the Standard clinical Guidelines, or in Martindale.

10.3 Particulars of tests which have been performed on laboratory animals and humans regarding the efficacy of the drug and the indications for which it will be used (pharmacological and clinical trials)

Details of studies on the following subjects shall be provided:

- ▶ **Pharmacodynamic studies** (*in laboratory animals or humans*)
 - Primary pharmacodynamics - primary action in target system.
 - Secondary pharmacodynamics - resultant action in target systems.

- Safety pharmacology - pharmacodynamics in non-target systems leading to side-effects.
- Pharmacodynamic drug interactions
- Individual pharmacodynamic studies shall include the following:
 - objective
 - identity and qualifications of key personnel involved
 - location(s) of study
 - experimental protocol including methodology and materials
 - summarised results and their statistical analysis
 - discussion and conclusions

▶ ***Efficacy and safety studies (in humans)***

- Controlled clinical efficacy studies
- Local and systemic tolerance studies to determine the maximum tolerable dose

▶ ***Individual clinical studies shall include the following:***

- Objectives (see classification above)
- Identity and qualifications of key personnel involved
- Location(s) of study
- Dates of study
- Design:
 - selection of subjects (inclusion, exclusion criteria)
 - selection of controls
 - selection of control treatment (if applicable)
 - number of subjects
 - response variables - end points
 - minimisation of bias - randomisation, blinding compliance.
- Treatments given:
 - identity and quality of the investigational and control products used
 - dosage used
 - duration of treatment
 - duration of observation periods
 - any concurrent treatments and their justification.
- Analytical methods for determining drug concentrations in body fluids, tissues
- Analysis of results including statistical analysis.
- Discussions and conclusions on efficacy and safety, including but not limited to:
 - suitability for Uganda in terms of any national treatment programmes
 - applicability of the clinical studies to the Ugandan population
 - adverse reactions observed and their relationship with the administered dose

10.4 Particulars of side effects, contra-indications, etc of the drug

The adverse effects of the product, the patients in which it should not be used, precautions before or during use in certain patients, shall be stated.

10.5 Data relating to the pharmacokinetics and bioavailability of the drug in laboratory animals and humans.

- ▶ Details of studies under the following topics shall be provided:
 - Absorption, distribution, metabolism, excretion characteristics
 - Relationships between pharmacokinetic characteristics and therapeutic and toxic effects
 - Pharmacokinetic drug interactions observed or predicted.
 - Methods of analysis used and their validation (see annex I)

10.6 Bioequivalence data for generics including full details of the reference product

Products which are copies of innovator products in terms of identity and amount of active ingredient(s) and formulation are generic products. Manufacturers of generic products claim the same indications for the generic products as those claimed for the innovator product. Such claims are based on the assumption that the generic product has the same efficacy as the innovator product.

For the benefit of the patient, this assumption has to be proven by the generic manufacturer in the registration application. The recognised way of proving the assumption is to show, *in humans*:

- ▶ that the active ingredient(s) in the two products reach systemic circulation at the same rate and to the same extent (comparable bioavailability/bioequivalence for systemic products), or
- ▶ that the finished products have the same pharmacodynamic actions, or
- ▶ that they produce similar therapeutic benefits, or
- ▶ that they differ only within specified limits (this constitutes a therapeutic equivalence study)

Therapeutic equivalence studies are often very expensive and it is therefore necessary to specify the products for which therapeutic equivalence studies are absolutely necessary, and those that may be exempted. In some cases comparative dissolution studies are an acceptable alternative to therapeutic equivalence studies.

Guidance that the applicant should follow on **presentation of reports** of therapeutic equivalence studies for generic products is as follows:

- 1) *The investigator should be identified and should sign and date the study report*
- 2) *The location of the studies should be identified*
- 3) *Type of equivalence study shall be defined*
 - ▶ Comparative bioavailability, urinary excretion, faecal excretion (bioequivalence studies)
 - ▶ Comparative pharmacodynamics where bioavailability is irrelevant, eg. for topicals
 - ▶ Comparative clinical trials, e.g. products with non-linear pharmacokinetics therefore not suitable for bioavailability studies
 - ▶ Comparative dissolution studies: comparison of dissolution profiles (concentration against time) for products with active ingredients classified as highly soluble and highly permeable according to the Biopharmaceutical Classification System.
- 4) *Evidence shall be provided that before the study began, the test and reference samples were proved to be:*
 - ▶ Stable: stability studies as in 8.5 above
 - ▶ Of the same strength and dosage form and intended for the same route of administration (pharmaceutical equivalence).
- 5) *The protocol of individual bioequivalence studies shall be described and shall include:*
 - ▶ Selection of subjects - description of rationale
 - ▶ Design:
 - *Number of subjects (minimum 12)*
 - *Age of subjects (must be >18yrs)*
 - *Feeding of subjects*
 - *Dosing of subjects*
 - *Collection of samples*
 - *A statement on whether it is a parallel or crossover design:*

May be a **parallel design**: one set of subjects is given the reference (innovator) product and another set the test (generic) product.

May be a **crossover design**: one set of subjects is given the test product and another set the reference product during the first period. This is followed by a washout period (generally 5 half lives of the drug) and then by a second period where the first set of subjects is given the reference substance and the second set the reference product.

For modified-release products a **replicate study** should be conducted (i.e. two crossovers) comparing the highest strength of the test and reference product in fasting subjects. In addition a non-replicate study comparing the highest strength of the test and reference products should be conducted in fed subjects.

- *Pharmacokinetic data to be determined are total exposure (AUC) and peak exposure (Cmax). All data should be presented, i.e. measured drug concentrations, calculated parameters (Cmax, AUC), mean values and final results*
- *Plasma concentration values should be log transformed.*
- *Statistical analysis of results: the Cmax and AUC values are analysed by analysis of variance (ANOVA).*
- *Validation of analytical methods*
- *Studies on metabolites where necessary*

6) *A discussion and conclusion on the results shall be given.*

- ▶ *Acceptance criteria for equivalence: for AUC and Cmax, the 90% confidence interval on the geometric mean ratio of test to reference products must fall within 80% - 125% of the geometric mean of the reference substance.*

7) *The protocol of individual comparative dissolution profile studies shall be described and shall include:*

▶ **Test conditions**

- Apparatus
 - basket method at 50/120 rpm, or
 - paddle method at 50/75 rpm
- Medium
 - aqueous medium, pH 1.2, 4.5, 6.8
 - for sparingly water soluble drugs: use of surfactants
 - 500 - 1000mL; 37°C ± 0.5°C
- Sampling time
 - 15 minute intervals until 85% dissolution (immediate release products)
 - 60 minutes, at 50% dissolution, and at 80% dissolution (for modified release products)

▶ **Results**

Dissolution profiles in different media (tables and graphs)

▶ **Statistical treatment**

$$f_1 = \left\{ \left[\sum_{t=1}^n (R_t - T_t) \right] / \left[\sum_{t=1}^n R_t \right] \right\} \times 100$$

$$f_2 = 50 \times \log \left\{ \left[1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where R_t and T_t are the cumulative % of dissolved active substance at each of the selected n time points.

f_1 is proportional to the average difference between the two profiles (difference factor)

f_2 is inversely proportional to the average squared difference between two profiles and measures the closeness between the two profiles (similarity factor)

Since the interest is to know how similar the profiles are, f_2 is used.

If the two products produce identical results at all time points, $f_2 = 100$.

If there is an average difference of 10% in the results at all time points results, $f_2 = 50$.

- ▶ *Acceptance criteria*
 - f_2 should be between 50 and 100

Notes on the Application of Bioequivalence Studies

1) Products for which **bioequivalence studies are necessary**

- ▶ Products where the innovator manufacturer changes the composition or manufacturing method of his original product.
- ▶ Products where the route of administration is changed from the original product.
- ▶ **Oral solid dose immediate-release products:**
 - a) Oral solid dose immediate-release products indicated for serious conditions requiring rapid and/or assured therapeutic response, as listed in Table 1 below
 - b) Oral solid dose immediate-release products with narrow therapeutic and/or safety indices as listed in Table 2 below
 - c) Oral solid dose immediate-release products whose active ingredients undergo incomplete absorption, non-linear pharmacokinetics or extensive pre-systemic or first-pass metabolism
 - d) Oral solid dose immediate-release products with a high ratio of excipients to active ingredients
 - e) Non-oral, non-parenteral products that are intended to undergo systemic absorption as listed in Table 3 below
 - f) Prolonged or modified-release oral solid dose products
 - g) Oral fixed-combination products.

2) Products for which **comparative dissolution profile studies are necessary**

- ▶ All oral solid dose anti-infectives:
 - a) Anti-protozoals including antimalarials
 - b) Antibacterials
 - c) Antifungals
 - d) Antivirals (note: anti-retrovirals require bioequivalence studies)

3) Products for which **bioequivalence studies are not necessary**

- ▶ Parenteral aqueous solutions with the same active ingredients, excipients and route of administration as the original product
- ▶ Oral products not intended for systemic absorption
- ▶ Oral solutions with the same active ingredients as the original product and with no excipients interfering with their absorption, and **not** containing active ingredients with narrow therapeutic and/or safety indices as listed in Table 2 below
- ▶ Products reformulated by the original manufacturer to change inactive ingredients like colouring agents, flavouring and preservatives, which do not interfere with bioavailability
- ▶ Gases

- ▶ Powders for reconstitution as solutions to be used as in parenteral or oral solutions above
 - ▶ Ophthalmic or topical aqueous solutions with the same active ingredient(s), similar excipients and similar quantitative composition as the original product
 - ▶ Inhalation liquid products containing the same active ingredients and with a similar quantitative composition as the original product.
- 4) Biowaivers based on dose proportionality:
When the highest strength of the generic product is bioequivalent to the highest strength of the innovator product, and other strengths are proportionally similar in formulations and the dissolution profiles are similar between the dosage strengths, biowaiver can be granted to lower strengths. Proportionally similar formulations are those in which:
- ▶ All active and inactive ingredients are exactly in the same proportion between strengths (e.g. tablet of 50mg strength has all the inactive ingredients exactly half that of tablet of 100mg strength, and twice that of 25mg strength).
 - ▶ For a high potency active pharmaceutical ingredient (up to 10mg per dosage unit), where the amount of active pharmaceutical ingredient in the dosage form is relatively low, the total weight of the dosage form remains nearly the same for all strengths (within $\pm 10\%$ of the total weight), the same active ingredients are used for all strengths, and the change in strength obtained by altering the amount of the active ingredients and one or more inactive and inert ingredients.
- 5) Biowaivers based on Biopharmaceutical Classification System (BCS):

A biowaiver based on BCS is one that considers solubility and permeability of the active pharmaceutical ingredient, as well as dissolution profile similarity of the multisource and comparator product in three media: 1.2 N HCl, pH 4.5 and pH 6.8. The BCS guidance recommends biowaiver only for class 1 drug products. However, biowaiver may be extended to:

- ▶ BCS class 3 drug products, if the multisource and comparator product are very rapidly dissolving (85% or greater in 15 minutes or less in pH 1.2, 4.5 and 6.8).
- ▶ For class 2 weak acids if the multisource product dissolves 85% or greater in pH 6.8 in 30 minutes or less and its profile is similar to comparator product in pH 1.2, 4.5 and 6.8.

Table 1: Oral immediate-release products indicated for serious conditions.

All antiepileptics	All contraceptive hormones
All antiarrhythmics	All hypoglycaemics
All antimigraine products	All opioid analgesics
All antiretrovirals	All oral anticoagulants
All beta-2 agonists for asthma	Glyceryl trinitrate

Table 2: Oral immediate-release products with narrow therapeutic and/or safety indices

Amphotericin	Methotrexate
Antiepileptics	Minoxidil
Anti-inflammatory steroids	Monoamine oxidase inhibitors
Azathioprine	Oral anticancer drugs
Clozapine	Pyrazinamide
Cyclosporin	Premedication (anaesthesia & surgery)
Digoxin	Quinidine
Ergotamine	Rifampicin
Ethambutol	Sertindole
Gold salts	Sulphasalazine
Isoniazid	Theophylline
Hydralazine	Verapamil

Table 3: Non-oral, non-parenteral products intended for systemic absorption

Suppositories	Transdermal patches
Systemic enemas	Systemic nasal sprays
	Systemic oral sprays

10.7 Notes

- a) With the exception of therapeutic equivalence testing requirements, applicants may request partial or total exemption from the testing requirements of Appendix IV of the application form if the drug being applied for is a single active ingredient generic or a pharmacopoeial generic combination product.

Literature from reputable publications on safety and efficacy, toxicology, pharmacodynamics, pharmacokinetics, shall be provided in lieu of testing.

- b) All the information provided in the information leaflet for the product shall be consistent with the information provided in Appendix IV

11. APPENDIX 5 (of Form NDA: R1)

11.1 References to literature shall be precise, quoting the year of publication and the relevant page(s). Photocopies of relevant literature may be attached.

A minimum of two samples of the final product for each package size being applied for must be provided in the form in which it shall appear on the market.

12. LIST OF ANNEXES

The following annexes are attached to these guidelines:

- 12.1 Annex I- Registration Fees Structure
- 12.2 Annex II- Guidelines for Submission of Amendments
- 12.3 Annex III- Guidelines to Analytical Method Validation

13. ADDITIONAL REFERENCES WHICH APPLICANTS SHOULD CONSULT

1. International Conference on Harmonization of Technical Requirements for registration of pharmaceutical products <http://www.ich.org>
2. U.S. Food and Drug Administration- Centre for Drug Evaluation and Research: <http://www.fda.gov/cder/index.html>
3. European Medicines Agency: <http://www.emea.eu.int/htms/human/epar/a-zepar.htm>
4. Therapeutic Goods Administration <http://www.tga.gov.au/>
5. WHO Prequalification of Medicines: <http://mednet3.who.int/prequal/>
6. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996: 114-154 (WHO Technical Report Series, No. 863)
7. Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1997: 15-177 (WHO Technical Report Series, No. 863).