

**GUIDELINES on the REGISTRATION of
TRADITIONAL MEDICINAL PRODUCTS
for HUMAN or VETERINARY USE IN UGANDA**
(1st Edition August 2001)

1. GENERAL

The NDA definition of traditional medicinal products is based on the World Health Organisation definition and is as follows:

Traditional medicinal products are finished, labelled medicinal products used in traditional systems of medicine, that contain as active ingredients parts of plants, or other plant material, or combinations thereof, whether in crude state or as processed plant preparations. Plant materials include juices, gums, fatty oils, and essential oils. Traditional medicines may contain excipients. Medicines containing chemically defined active substances, including chemically defined, isolated constituents of plants are not traditional medicines.

Some traditional medicines may also contain natural organic or inorganic active ingredients, which are not of plant origin.

All applications for registration of traditional medicinal products should therefore conform to this definition.

- 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 fee shall accompany each complete application form, ie. US\$ 500 for a product manufactured outside Uganda, US\$ 300 for a locally repackaged foreign product and US\$ 200 for a product manufactured in Uganda. Subsequent applications to amend any part of the application shall be accompanied by US\$ 50 fee per change. The guidelines on submission of amendment applications shall be followed.
- 1.4 Registration procedures shall commence only if Form NDA: R3 or NDA: R4 with its appendices has been properly completed. Only the information required in the appendices should be furnished.
- 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: nda@imul.com

- 1.6 **Payment of fees** can be made:

- a) by Bank Transfer to:

National Drug Authority Account no: 0240060034201
Stanbic Bank Uganda Limited, Kampala

- b) by bank draft in favour of National Drug Authority

- 1.7 The requirements outlined in these guidelines shall apply to all imported products, and all locally manufactured products intended for sale by wholesale or retail sale to the general public. Products compounded by local traditional herbal practitioners and prescribed and dispensed directly by them to their patients within their localities shall be exempted from registration.

2. APPLICANT

- 2.1 Application for the registration of a drug shall be made only by:
- the patent holder
 - the manufacturer
 - a distributor authorised by the manufacturer or patent holder
 - an authorised Local Technical Representative (LTR) of the manufacturer or patent holder (see section 5 below)
- 2.2 The name, physical address, telephone number, fax number, and e-mail address of the applicant shall be provided.

3. 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 **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.
- 3.3 **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 the marks "Amp-250" on the side', 'pink film-coated tablets with word "PAN" embossed on one side' etc.
- 3.4 **Pack size(s) applied for** shall be those intended for marketing and should be the ones submitted as samples
- 3.5 **Main indications** shall be those conditions for which the product is normally used and for which marketing authorisation is being sought. The applicable system of medicine should be mentioned, eg. Ayurveda, Sidda, Unani, Chinese traditional medicine, 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 (INN)/generic name or botanical name where appropriate.
 - iii) quantity of active ingredient per dosage unit
 - iv) total contents of container
 - v) date of manufacture
 - vi) date of expiry
 - vii) batch number
 - viii) storage conditions
 - ix) name and address of manufacturer

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.

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, or botanical name where appropriate.
- 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 over-dosage
- 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 addresses, 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.

5. AUTHORISED REPRESENTATIVE IN 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 applicant, 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 registered pharmacist or herbal/complementary medicine practitioner working for and/or authorised by the applicant. The designation and qualification of the signatory shall be stated.

7. APPENDIX 1 (of Forms NDA: R3 and R4)

7.1 SPECIFICATIONS OF THE PACKAGING MATERIAL

a) Primary (inner) container

This is the container in immediate contact with the drug. Detailed specifications of the type, nature, size and grade of the primary container shall be given including the method of closure and, for liquid products, the fill volume. Specifications for glass containers for parenteral products, aqueous solutions and rubber closures for containers for parenteral products are as per BP, USP or Ph. Eur. specifications.

b) Outer packaging

Where applicable, the same requirements as above shall apply.

7.2 COMPOSITION OF THE PRODUCT

a) *The active ingredient(s)* shall be the common or traditional name of the processed plant material(s), or other natural material(s) in the product, possessing the medicinal properties responsible for the product's medicinal action (indications). Such processed material is derived from crude plant parts or crude plant materials, or other natural materials by processes such as extraction, distillation, comminution and heat treatment.

b) *Source* of the raw material (processed material) shall be the crude part of the plant used to obtain the processed plant material described above. The common name of the plant shall be stated. For other natural raw materials, the relevant source (eg. type of rock used, part of animal, etc) shall be stated.

c) *Quantities* of the active ingredients (processed material) shall be given in terms of the content per dosage unit, eg. mg/tablet, mg/ml, etc.

d) *Species of plant* used shall be the botanical name of the plant used.

e) *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 Forms NDA: R3 and R4)

8.1 **Raw material specifications and details of analytical methods** to test compliance to these specifications should be described. Where references to pharmacopoeial specifications and analytical methods are given, full photocopies of those references (monographs) should be supplied. Such pharmacopoeias include the British Herbal Pharmacopoeia, Ayurvedic Pharmacopoeia of India, or the list of WHO herbal monographs.

In all other cases specifications and analytical methods should be described for the processed material and the crude material from which it is processed as follows:

(a) **Crude plant parts or plant material/non-plant material:**

- ▶ Definition:
 - name of plant
 - part of plant
 - nature/condition of material: whole, powdered, fresh, dried, etc.

- ▶ Authentication: confirmation of:
 - Correct geographical origin
 - Correct stage of growth
 - ▶ Freedom from foreign matter:
 - other plant parts or materials
 - soil, stones, dust
 - insects and other animal matter(as determined by microscopy, macroscopy, chromatography - see below).
 - ▶ Microscopic characteristics confirming identity:
 - qualitative features
 - quantitative features, eg. stomatal number
 - ▶ Radioactive contamination limits: arising from environmental pollution or microbial decontamination procedures.
 - ▶ Assay: for materials containing constituents of known therapeutic activity, or known unique (marker) compounds. Non-specific assay methods for groups of compounds may be used where specific assay methods are not available for single compounds.
 - ▶ Conformation to a pharmacopoeial monograph
 - ▶ A copy of the manufacturer's or supplier's certificate of analysis shall be attached to confirm conformation to these specifications
- (b) **Processed plant materials/non-plant materials (extracts, tinctures, comminutions etc):**
- ▶ Definition: liquid, solid, etc
 - ▶ Organoleptic characteristics:
 - macroscopy
 - smell
 - taste
 - texture
 - colour
 - ▶ Chromatographic profile using more than one method:
 - to confirm presence of unique compounds (markers)
 - to confirm characteristic TLC chromatogram
 - to confirm characteristic HPTLC chromatogram (TLC + densitometry = HPTLC)
 - ▶ Water content (for hygroscopic materials)
 - ▶ Ash values: indicate extent of contamination with inorganic material. Determined by incineration. Values include acid insoluble and sulphated ash
 - ▶ Volatile matter: for plants containing volatile oils. Determined by steam distillation
 - ▶ Heavy metal limits: from environmental pollution and pesticides
 - ▶ Microbial contamination limits: microbial contamination arises from cultivation, harvesting, processing and storage:
 - confirmation of absence of *E. coli*, *S. aureus*, *P. aeruginosa* and *salmonella*

- limits for aflatoxins (fungal toxins)
- ▶ Residual solvents from processing
- ▶ Pesticide residue limits: arising from cultivation (FAO and WHO limits)
- ▶ Extractive values: extraction by different solvents indicates proportion of polar and non-polar components
- ▶ Assay: for materials containing constituents of known therapeutic activity, or known unique (marker) compounds. Non-specific assay methods for groups of compounds may be used where specific assay methods are not available for single compounds

Notes:

- i) A copy of the manufacturer's or supplier's Certificate of Analysis (CoA) shall be attached to confirm conformation to these specifications.
 - ii) Where unprocessed crude material is used as raw material, the specifications and tests described in 8.1(b) above shall also apply to the crude material.
 - iii) Omission of any of the above specifications and tests for any crude or processed active raw material should be well-justified.
- (c) **Inactive ingredients:** as per pharmacopoeial monograph, or in-house monographs where no pharmacopoeial monographs exist.
- 8.2 Comprehensive details of the **procedures involved in the various stages of manufacture**, including packaging (eg. a description of the type of equipment, duration of treatment, etc.) shall be given.
- 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.
- 8.4 **Summarised specifications of the final product** shall be given, ie. the acceptable limits of all the physical, chemical and (where applicable) microbiological parameters. A full description of analytical and other control procedures carried out to ascertain the final product specifications shall also be given. The following specifications and relevant analytical methods shall be described:

1) **Specifications and test methods (for all dosage forms)**

- ▶ Description of dosage form
- ▶ Identity
- ▶ Assay: specific or non-specific; stability-indicating
- ▶ Impurities
 - degradation product of active raw materials
 - microbial limits

2) **Additional tests for specific dose-forms**

Hard gelatin capsules and tablets (coated & uncoated)

- a) Dissolution/Disintegration
- b) Hardness & friability
- c) Uniformity of content and mass (dosage units)
- d) Water content

Oral liquids

- a) Uniformity of content and mass
- b) pH

- c) Microbial limits
- d) Antimicrobial preservative content
- e) Antioxidant preservative content
- f) Extractables from container/closure system
- g) Alcohol content
- h) Dissolution for suspensions and powders for suspension
- i) Redispersibility for suspensions.
- j) Viscosity for suspensions or viscous solutions
- k) Specific gravity for suspensions or viscous solutions
- l) Water content for powders for reconstitution.

Where analytical procedures in various parts of the application coincide, these procedures may be reflected in one part and may be subsequently referred to, provided that the relevant page and paragraph are clearly identified. Reference only to standard books of reference will not be acceptable.

Omission of any of the above specifications and tests should be well-justified.

8.5 **Evidence of Stability** shall be submitted as follows:

▶ ***Stability studies on imported finished product should:***

- i) be on the market pack
- ii) have a detailed protocol
- iii) have summarised results
- iv) have conclusions on:
 - proposed storage conditions
 - proposed shelf life
 - in-use storage conditions and shelf life

▶ ***Labelling recommendations shall be stated as follows:***

- Store under normal storage conditions (15°C - 30°C)
- Store between 2°C - 8°C (ie. refrigeration, no freezing)
- Store below 8°C (ie. refrigeration)
- Store between -5°C - 0°C (ie. in a freezer)
- Store below -18°C (ie. in a deep freezer)

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

▶ ***Stability studies on local finished product:***

- all local products shall have a shelf life of not more than one year.
- copy of certificate of analysis one year from the date of manufacture shall be submitted

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) sterilisation records
- f) Certificates of Analysis for the finished product.

9. APPENDIX 3 (of Forms NDA: R3 and R4)

9.1 Evidence of safety in use

- a) *For products of long-term traditional use:* bibliographical (documentary) evidence of safety should be submitted including the following:
 - i) Evidence of long-term use (in terms of decades)
 - ii) Specification of the system of traditional medicine, disorders treated, numbers of users and countries of use (as found in literature, monographs, etc)
 - iii) Indication of the lack of toxicity problems over the documented period of time
 - iv) If toxicity problems are revealed by the documentation, toxicological studies should be done to determine safe dosage, and risk assessment made and presented in the dossier
 - v) Details of the potential for misuse, abuse or dependence
 - vi) Bibliographical evidence sources include reference literature (textbooks, journals etc), case reports, pharmacopoeial monographs
 - vii) In the case of local products where there may not be much bibliographical evidence available, the applicant shall write a summary clearly confirming the safety of the product.
- b) *For foreign products where there is no bibliographical evidence of safety in long-term use:* toxicological studies proving safety are necessary, and should be submitted in the dossier.

9.2 Evidence of efficacy in use

Evidence should be submitted as follows:

- a) Pharmacological and clinical effects of active ingredients and their active constituents if known should be described, and should be relevant to the main indications of the product
- b) For products with long-term traditional use, used for minor disorders or non-specific indications or for prophylactic use: bibliographical evidence of efficacy is should be submitted, eg. literature (textbooks, journals etc), case reports, pharmacopoeial monographs
- c) For products without bibliographical evidence of efficacy in traditional use: reports of clinical studies proving efficacy
- d) Combination products: for new combinations of active ingredients, the therapeutic justification, compatibility and dose range should be given. For well established combinations, photocopies of references in traditional texts (eg. Ayurveda, traditional Chinese) will be acceptable as evidence of efficacy
- e) In the case of local products where there may be little or no bibliographical evidence available, the applicant shall write a summary clearly explaining the efficacy of the product.

10. APPENDIX 4 (of Forms NDA: R3 and R4)

The following shall be submitted:

- 10.1 The proposed patient information leaflet for products intended for self- medication
- 10.2 The proposed prescriber information leaflet for intended prescription-only products
- 10.3 Any proposed advertising material
- 10.4 Two samples of each pack size intended for marketing
- 10.5 A copy of marketing authorisation in the country of manufacture