GUIDELINES FOR INTRODUCING A LOCALLY MANUFACTURED NEW PHARMACEUTICAL PRODUCT ON THE UGANDA MARKET

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INTRODUCTION

National Drug Authority (NDA) was established in 1993 by the National Drug Policy and Authority Statute which in 2000 became the National Drug Policy and Authority (NDP/A) Act, Cap. 206 of the Laws of Uganda (2000 Edition). The Act established a National Drug Policy and National Drug Authority to ensure the availability, at all times, of essential, efficacious and cost-effective drugs to the entire population of Uganda, as a means of providing satisfactory healthcare and safeguarding the appropriate use of drugs.

The Vision of NDA: "A Uganda with safe, effective and quality medicines and healthcare products".

The Mission of NDA: "Promoting and protecting public health through the effective regulation of human and animal medicines and healthcare products".

The National Drug Policy and Authority Act, Sections 2(d) and 5(e) mandated NDA to exercise control on manufacture, production and on the quality of drugs. One of the means of achieving this is through compliance with Good Manufacturing Practice (GMP) requirements. These guidelines shall therefore be used for assessment of pre-manufacturing and pre-registration of a pharmaceutical product that is manufactured in Uganda..

Local and foreign manufacturers of pharmaceutical products shall be subjected to periodic GMP inspections by NDA, as per *Guidelines on Good Manufacturing Practice for Medicinal Products Part 1*, Doc. No.: INS/GDL/001- (Part 1), and those that are GMP compliant shall be issued with GMP compliance certificates.

Objective of these guidelines

To guide the local pharmaceutical manufacturers on the requirements for pre-manufacture and pre-registration of a pharmaceutical product that they intend to manufacture, register and market in Uganda.

Policy

These guidelines are developed in accordance with:

a) The National Drug Policy and Authority Act Cap 206, Sections 2(d): *"to improve government regulation and control on manufacture, production, importation, exportation, marketing and use of drugs"; and Section 5(e): "control the quality of drugs".*

b) The Statutory Instruments No. 35; The National Drug Policy and Authority (Licensing) Regulations, 2014:

Section 19(2*): "A manufacturer who manufactures drugs in Uganda or outside Uganda for importation into Uganda shall comply with the Good Manufacturing Practice Guidelines adopted by the Authority".*

Scope of these guidelines

These guidelines apply to all new pharmaceutical dosage formulations that are intended to be manufactured in Uganda.

The guidelines do not apply to new pharmaceutical dosage formulations for manufacturers outside Uganda; and to herbal/traditional medicinal preparations because these are still at notification level.

Interpretation

The definitions given below apply to the words as used in these Guidelines. They may have different meanings in other contexts.

Batch (or lot): A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity. For the control of the finished product, a batch of a medicinal products comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.

Batch records: All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Finished product: A finished dosage form that has undergone all stages of production, including packaging in its final container and labeling.

In-process control: Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Manufacture: All operations of purchase of materials and products, production, packaging, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

Manufacturer: A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

Marketing authorization (product licence, registration certificate): A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf-life.

Medicinal products: Any medicine or similar product intended for human or veterinary use, which is subject to control under health legislation in the manufacturing or importing country.

Packaging material: Any material employed in the packaging of a medicinal products, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Packaging: All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Pharmaceutical product: Any medicine intended for human use or veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

Production: All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to its completion as a finished product.

Qualification. Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word “validation” is sometimes extended to incorporate the concept of qualification.

Specification: A document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

Validation protocol (or plan): A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process or a part thereof for routine use.

Validation report: A document in which the records, results and evaluation of a completed validation program are assembled. It may also contain proposals for the improvement of processes and/or equipment.

Validation: Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

1. Information to be provided by a local manufacturer to NDA before start of manufacturing of a new pharmaceutical product

The manufacturer shall inform National Drug Authority (NDA) in writing about the intention of producing a new pharmaceutical product and provide the following:

1.1 The name and description of the product including physicochemical and biological properties of the drug substance.

1.2 The Master formula, product components including reasons for inclusion.

1.3 Where the product includes a raw material of herbal nature, an impurity profile and heavy metal test report will be required.

1.4 Information on compatibility of the different components. The compatibility of the drug substance with excipients, excipient with other excipients, where relevant (for example, combination of preservatives in dual preservative systems) should be established.

1.5 Master batch manufacturing, master batch packaging and master batch testing protocols of the product.

1.6 A list of equipment intended to be used in manufacturing and quality control.
Where the local pharmaceutical manufacturer has no capacity to carry out a particular quality control test of either the inputs or the finished product, such a test shall be outsourced to a competent quality control laboratory as per chapter 7 (Outsourced Activities) of the NDA GMP guidelines, doc. no. INS/GDL/001. Copy of the contract should be submitted to NDA.

1.7 The entire manufacturing process should be clearly described including all the necessary controls. The selection of the controls, the manufacturing process and its appropriateness for the formulation should be explained. Manufacturing process flow chart clearly showing the stages at which in-process controls are done should also be provided.

1.8 The choice and rationale for selection of the container-closure system and the packaging materials for the pharmaceutical product should be provided with specifications. Consideration should be given to the intended use of the drug product and the suitability of the container closure system for storage and transportation.

1.9 Artwork or actual specimen for the packaging and labeling materials to be used.

1.10 Validation protocols (for process, analytical methods and cleaning validation).

1.11 Information about the premises and support systems (pharmaceutical water system, air handling system, compressed air system and stability determination system).

2. Pre-manufacturing information assessment by NDA

2.1 NDA shall assess the information provided in 1 above in relationship to already licensed products of the manufacturer, if any, and verify that the manufacturer is able to manufacture the product according to the NDA Good Manufacturing Practice guidelines, doc. no. INS/GDL/001.

2.2 The manufacturer shall be informed of the results of the assessment and where necessary may present proforma invoices for importation of raw and packaging materials to enable startup of the production trials.

2.3 The manufacturer will be allowed to manufacture a minimum of three consecutive batches of the product for validation purposes and thereafter submit the executed batch manufacturing, batch packaging and batch testing records to NDA for assessment.

2.4 Process validation should be undertaken to establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities. The product life cycle should be taken into consideration while carrying out this process.

2.5 Batches manufactured for process validation should be the same size as the intended commercial scale batches. The use of any other batch sizes should be justified.

2.6 The assigned shelf life of the new finished product from the three batches shall not exceed 24 months.

2.7 When process validation is completed, the manufacturer should start accelerated stability studies of samples selected from the manufactured batches. The stability chamber set conditions should be 40°C ± 2°C, 75% RH ± 5% RH, for 6 months.

3. Post-manufacturing information assessment by NDA

3.1 At the end of the process validation phase, the manufacturer shall submit to NDA, the following information for a minimum of three consecutive batches:

a) executed batch manufacturing records;

b) batch packaging records;

c) batch testing records;

d) Reports of process validation, cleaning validation, and analytical method validation (in case the laboratory uses a non-pharmacopeial analytical method).

e) finished product samples (refer to Appendix 1 for Sampling Plan).

3.2 NDA shall assess the information submitted by the manufacturer for correctness and completeness.

3.3 NDA shall evaluate the information submitted and test the samples from the three consecutive batches; and inform the manufacturer of the results of the assessment.

3.4 If the results of analysis show that samples for all the three consecutive batches pass the required specifications, and all queries which may have been raised by NDA are addressed by the manufacturer, NDA shall grant pre-marketing authorization and inform the local pharmaceutical manufacturer in writing.

3.5 Permission shall then be granted to the local manufacturer to proceed with production of the pharmaceutical product and sell on the Uganda market, including the first three consecutive batches.

3.6 The Manufacturer shall proceed with accelerated and long-term stability studies and apply for registration of the product after production of not more than six batches or within six months from the date of pre-marketing authorization, whichever comes first.

3.7 Where no significant change is observed in the finished product stability studies at accelerated and long-term conditions for at least six months, data covering a minimum of six months should be submitted to NDA along with the product dossier in CTD format, for evaluation and assessment for registration of the product.

3.8 NDA will assess the product dossier as per the NDA *Guidelines on Submission of Documentation for Marketing Authorization of a Pharmaceutical Product for Human Use*, Doc. No. DAR/GDL/004 and shall register the product and grant marketing authorization, if all information submitted complies with the registration guidelines.

3.9 A new pharmaceutical product shall not be allowed on the market after six months from the date of pre-marketing authorization or beyond production of the sixth batch (including the first three consecutive batches), whichever comes first, unless it has been registered by NDA.

References

Guidelines on Good Manufacturing Practice for Medicinal Products Part 1, Doc. No.: INS/GDL/001- (Part 1), Revision Number 2, National Drug Authority, Kampala, Uganda.

Guidelines on Good Manufacturing Practice for Medicinal Products Part 1, Doc. No.: INS/GDL/001- (Annexes), Revision Number 1, National Drug Authority, Kampala, Uganda.

Guidelines on Submission of Documentation for Marketing Authorization of a Pharmaceutical Product for Human Use, Doc. No. DAR/GDL/004, Revision Number 2, National Drug Authority, Kampala, Uganda.

Appendices

Appendix 1: Sampling plan for drugs

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SAMPLING PLAN FOR DRUGS

Sr. No.	**Dosage Form**	**Minimum Sample Size (per batch/lot)**
1	Tablets	100 tablets
2	Capsules	100 capsules
3	Oral solution / suspension *(bottles of 100 ml and above)*	10 bottles
4	Oral solution / suspension *(bottles below 100 ml)*	20 bottles
5	Powder for oral suspension	20 bottles
6	Sterile solution injection / IV fluids / eye drops	60 ampoules / vials / bottles
7	Sterile suspension injection	20 ampoules / vials
8	Sterile powder for injection	25 vials
9	Streptomycin sterile powder for injection	50 vials
10	Eye ointment	12 tubes
11	Creams / gels / ointments (for topical use)	5 tubes / containers
12	Powders packed in sachets	25 sachets

Notes:

1. All samples must be picked in their intact (un-opened, un-tampered) primary packaging materials (primary containers).
2. For tablets and capsules where the primary packaging (primary container) contain more than 100 tablets or capsules, the entire container should be sampled.
3. The recommended storage conditions should be observed during sampling and delivery of the samples to the laboratory.
4. The minimum sample sizes shown above are derived with consideration for the requirements of the out-of-specifications (OOS) results investigation procedure and possible re-testing in case results are disputed by the client.

Document Revision History

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
10th March 2000	0	Not on record	Deus Mubangizi	First issue
24th Jan. 2018	1	INS/GDL/004	Authors: Conrad Mark Denis Mwesigwa Peter Ssali	a) Revised the title of the document, changed format, changed document numbering system. b) Revised the entire guidelines so as to comply with the product registration requirements in the NDP&A Act cap 206 and the Statutory Instruments No. 35 *The National Drug Policy and Authority (Licensing) Regulations*, 2014; and the guidelines on Submission of Documentation for Marketing Authorization of a Pharmaceutical Product for Human Use, Doc. No. DAR/GDL/004. c) Added information on stability studies and an appendix for sampling plan for drugs. d) *Replaced "provisional registration"* with *"pre-marketing authorization".* e) Replaced *"At the end of 3 months.."* with *"..within six months from the date of pre-market authorization.."* in order to allow the manufacturers enough time to complete accelerated stability studies. *f)* Replaced *"Executive Secretary/Registrar*" with *"Secretary to the Authority".*

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