QUALITY CONTROL LABORATORY

LIBERIA MEDICINES & HEALTH PRODUCTS

REGULATORY AUTHORITY (LMHRA)

King's Farm, Careysburg
Montserrado County
Republic of Liberia

GUIDELINES FOR

QUALITY ASSURANCE/QUALITY CONTROL OF MEDICINES & HEALTH PRODUCTS

Version No. 001

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TABLE OF CONTENTS

ACKNOWLEDGEMENT

The writing of this guideline is an outcome of a five (5)-day retreat for senior staff of the Liberia Medicines and Health Products Regulatory Authority (LMHRA). We herein acknowledge the ingenuity, far-sightedness and leadership role of Pharm. Keturah C. Smith, Managing Director of LMHRA, which led to the successful convening of the retreat.

We also acknowledge the organizational skills and guidance of the 2020 Retreat Committee led by Dr. Thomas B.L. Kokulo who is the Deputy Director of the Inspectorate Department of LMHRA. We salute the retreat participants for the useful comments during the deliberations of the retreat. Their contributions during the deliberations and the resolution derived from the Retreat helped in the crafting of this regulatory guidance document.

Much recognition is given to the Guideline Drafting Team which includes Pharm. Diana M. Jeator, Deputy Director of QC Lab; Pharm. David P. Namakpeh, Quality Assurance Manager; Pharm. Matu K. Fayiah-Nyanti, Deputy Quality Assurance Manager; Mr. Albert D.Z. Gbusseh, Deputy Quality Control Manager, and Mr. Alexander E. George, Quality Control Manager, who played the leadership role in this process. Our heartfelt thanks also go to Pharm. Akoi Fahnbulleh, Director of the QC Lab for his encouragement and moral support to the Guideline Drafting Team.

We also acknowledge and give recognition to the World Health Organization (WHO) and the International Committee on Harmonization (ICH) for making available documents which were used as resource materials in the compilation of this guideline.

Most importantly and above all else, we sincerely give thanks and praises to the Almighty God for endowing us with the insight, resourcefulness and strength to draft this guideline. The guideline, along with other quality documents, shall constitute the legal basis for the quality assurance and quality control activities of the QC Lab.

The LMHRA QC Lab shall welcome comments/suggestions for improvement of this guideline during its implementation.

LIST OF ABBREVIATIONS

CoA	Certificate of analysis
GMP	Good manufacturing practice
ICH	International Conference on Harmonization
INN	International Non-proprietary Name
ISO	International Organization for Standardization
LMHRA	Liberia Medicines & Health Products Regulatory Authority
MA	Market Authorization
PMS	Post-Market Surveillance
QA	Quality Assurance
QC	Quality Control
WHO	World Health Organization

GLOSSARY

For the purpose of this guideline the following terms shall be defined as follows:

Act: a **law** or formal decision made by a parliament or other group of elected **law**-makers

Active pharmaceutical ingredient: Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings.

Allopathic medicine: medicines which are used as medication or in surgery to treat or suppress symptoms or the ill effect of disease.

Batch number: a designation that is printed on the drug label that allows the history of its production to be traced. (Also known as ***lot number***)

Biological sample: A specimen such as blood, urine, tissue or vaccine obtained from humans.

Certificate of analysis: an authenticated document that is issued by a Quality Control Laboratory which ascertains that a product has met its pre-determined product release specification(s) and quality.

Comparator product: a pharmaceutical product with which the multisource (generic) product is intended to be interchangeable in clinical practice or as a reference in the investigation of the product quality.

Containment: a measure that limits or prevents the interaction of a drug product with its packaging material.

Label = 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 product.

Detection limit: *the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.*

Excipient: an inactive substance that serves as the vehicle or medium for a drug or other active substances.

Falsified medicines: medicines disguised as authentic but may contain ingredients of bad or toxic quality, or in the wrong dosage.

Finished product: the medicinal product that has undergone all stages of production, including packaging in its final container.

Herbal medicines: products made from botanicals, or plants, that are used to treat diseases or to maintain health.

ISO accredited laboratory: a laboratory that has met all requirements of ISO 17025 and is deemed technically competent to produce calibration and testing results.

Labeling: the process by which the manufacturer supplies information related to identification, technical description, and use of a drug (excluding shipping documents) by writing, printing or affixing graphic design to the drug product or on any of its containers or wrappers.

Linearity: the ability of an analytical procedure (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

LMHRA Hearing Board: a panel of experts with varying skills or knowledge in pharmacy, quality management system, law and ethics charged with the responsibilities to handle complaints arising from customers or against customers.

Manufacturer: a person or company which is responsible for designing, manufacturing, assembling, processing, labeling, packaging, refurbishing or modifying a drug, or for assigning to it a purpose, whether those tasks are performed by that person or on his/her behalf, and sells medicines under his/her own name, or under a trademark, design, trade name or other name or mark owned or controlled by the person.

Package insert: a document included in the package of a medication that provides information about that drug and its use.

Packaging: the collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use.

Parameters: characteristics which can be determined by analysis/testing and can be used to define the quality of the medicinal product.

Post-Market Surveillance: the practice of monitoring the safety of a pharmaceutical product or medical device after it has been released on the market.

Precision: the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions.

Market Authorization: is the process of scientific and regulatory review to evaluate the safety and effectiveness of medicinal or other health products.

Primary package: the packaging in direct contact with the product itself and which protects and preserves the product.

Quality assurance: a set of activities for ensuring quality in the processes by which product quality is assessed.

Quality control: a set of activities for ensuring quality in the pharmaceutical products (medicines and all other health products).

Quarantined product: pharmaceutical products put aside or removed from sale to avoid contamination of other products or for investigative purpose.

Quaternary package: the fourth protective layer of packaging of a pharmaceutical product.

Range: the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

Repeatability: the precision under the same operating conditions over a short interval of time.

Robustness: a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Sample schedule: a document specifying the number of units of a particular dosage form of medicine to be collected during sampling.

Sampling: the selection of medicinal or other health products from a targeted batch of products already imported into the country at the warehousing facility(ies) of the importer.

Secondary package: the second protective layer of packaging of a pharmaceutical product.

Specification: an outline of the acceptance limits/criteria for a particular method of analysis

Substandard product: medicinal products that fail to meet either their quality standards or specifications, or both.

System suitability: the checking of a system, before or during analysis of unknowns, to ensure system performance.

Tertiary package: the third protective layer of packaging of a pharmaceutical product.

Validation protocol: a written statement or documented program or procedure used to provide a high degree of quality assurance that a specific process, method, or system is consistently producing results that meet pre-determined acceptance criteria.

Visual inspection: the use of the human senses to ensure the safety of medicines in their containers.

STATEMENT FROM THE MANAGING DIRECTOR

As a National Regulatory Agency for medicines and health products, the Liberia Medicines and Health Products Regulatory Authority is responsible to ensure the efficacy, quality and safety of all medicines and health products that circulate on the Liberian market. Additionally, it is incumbent upon the Authority to adequately disseminate relevant information for public consumption, and create a working tool for utilization by the public.

Against this background, these guidelines have been developed to provide guidance for all Pharmaceutical entities in Liberia.

I appreciate the contribution of the Quality Control Laboratory and the team of validators for their guidance in the development of the Quality Control and Quality Assurance Guidelines.

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LIBERIA MEDICINES AND HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

INTRODUCTION

The 2010 Act of the National Legislature which is the legal basis for the activities of Liberia Medicines and Health Products Regulatory Authority (LMHRA) provides for a Quality Control Laboratory responsible to conduct testing of all medicines and health products circulating the commerce of Liberia. This is intended to ensure that these medicines and health products are effective, of good quality and safe for use by the general population of Liberia.

The testing activities of the QC Laboratory are performed via quality assurance and quality control.

Quality assurance (QA) is a set of activities for ensuring quality in the processes by which product quality is assessed. The activities focus on identifying defects in the actual products produced. This is aimed at preventing defects in the Quality Management System or identifying the defects and ensuring that the defects are corrected. QA is a managerial tool.

Quality Control (QC) is a set of activities for ensuring quality in the pharmaceutical products (medicines and all other health products). Medicine's quality control testing independent of manufacturers is an important tool of medicines regulation. The LMHRA QC Lab performs independent quality control testing of all medicines.

The QC Lab, as a part of the regulatory body (LMHRA), performs post-production testing for different reasons and at various phases of the medicine's life. Testing is performed for the following reasons:

- Pre-registration – testing of samples submitted for registration;
- Pre-marketing of all batches of a product imported;
- Post-market surveillance;
- Special request

The medicines under consideration in this guideline are both allopathic and herbal medicines. This guideline considers all quality assurance/quality control activities involved during the submission of products for pre-registration testing, sampling at the importer's warehouse for pre-market and post-market surveillance testing. It also considers submission to and receipt of the samples by the QC Lab, documentations to be presented at the QC Lab, release of test results from the QC Lab, challenging of test results from the QC Lab and safety considerations such as packaging and labeling requirements, package inserts, sample handling and transportation and storage conditions.

It is the responsibility of all stakeholders (including the importers) to read and digest the contents of this guideline in order to remain in full regulatory and statutory compliance.

CHAPTER 1 QUALITY ASSURANCE/QUALITY CONTROL OF ALLOPATHIC MEDICINES

1.1. Product Submission for Pre-Registration Testing

Product registration at LMHRA begins with the submission of product dossiers to the Evaluation and Registration Department. The submission of dossiers is accompanied with the submission of the relevant product by the manufacturer.

For allopathic medicines (medicines which are used as medication or in surgery to treat or suppress symptoms or the ill effect of disease), the following are the requirements for the submission of products to the Evaluation and Registration Department for onward submission to the QC Lab of LMHRA:

- The product in its full quantity as specified in the sample schedule;
- The comparator product for reference;
- The method of analysis of the product if it is non-compendia (i.e., in-house);
- The certificate of analysis (CoA) of the finished product;
- The stability study data for the product;
- The manufacturer's method if this method is not contained in any of the compendia.
- The validation protocol and report for the in-house method of analysis of this product;
- The reference standard used for this in-house method where applicable.

Since the QC Lab must conduct full compendia test for all products submitted for registration, the duration of fast-track testing shall be at most two (2) months as of the date of submission of the product to the QC Lab. The duration of regular testing shall be at most three (3) months as of the date of submission of the product to the QC Lab.

If the manufacturer fails to submit **any** of the above-mentioned requirements, the product shall be rejected for analysis by the QC Lab.

1.2. Sampling

During sampling, medicinal or other health products are selected from a targeted batch of products already imported into the country at the warehousing facility(ies) of the importer. The selected batch is taken to the QC Lab to verify quality as claimed by the manufacturer. The information/results obtained from quality testing is used to draw conclusions or make inferences about the product or batch quality. Sampling is conducted for both pre-market authorization and post-market surveillance to ensure products maintain their quality throughout their shelf-life.

LMHRA QCL does not perform sampling on its own. However, the laboratory collaborates with the Inspectorate Department of LMHRA on sampling parameters such as sample size or guidance for a particular sampling exercise. Also, personnel from the Laboratory may be physically involved in sampling based on the request of the LMHRA top management, the Inspectorate Department or under special considerations. The Laboratory, however, exerts no direct control over such sampling and does not have responsibility for the sampling.

In any sampling activity, the importer or the entity at which sampling is conducted is under obligation to co-operate with the sampling team and provide all relevant information during the process. The sampling team will check to ensure that the sample storage areas have adequate light and ventilation and the samples are arranged to satisfy the requirements for safety as well as any special ones arising from the characteristics of the material being sampled. The sampling team shall observe and record all findings during the sampling exercise.

All samples must be collected in their full packages – primary, secondary, tertiary and quaternary (whatever is applicable). That is, each sample must be collected in its outermost package along with the inner package(s). The importer/entity should ensure that the appropriate packaging, labeling and storage requirements as contained in **Chapter 4** of this guideline are followed.

The appropriate sample schedule must be observed during the sampling exercise. For market authorization, the importer must provide adequate samples as spelled out in the sample schedule without any charge/cost to the sampling team. For post-market surveillance, the sampling team shall procure the required quantities of samples from the importer/entity consistent with the price tag on each sample in the store.

1.3. Sample Schedule

The sample schedule for pre-market analysis shall be the same for post-market surveillance, but slightly different for pre-registration. Customers are required to check with the Department of Evaluation and Registration for information about the sample schedule released by the QC Laboratory for MA & PMS, and that for registration of allopathic medicines.

1.4. Submission and Receipt of Samples

The submission to and receipt of samples by the QC Lab shall be guided by the following requirements:

1. *The samples submitted to the QC Lab must be in their original commercial package(s) and in their correct quantities as specified in the Laboratory's Sample Schedule.*
2. *The labels on all packages of the sample must be indelibly and legibly printed and words properly spelled.*
3. *All information contained on secondary and tertiary packages MUST be constant with the primary package.*
4. *For powder products containing their diluents with different batch numbers, these products MUST be paid for separately and shall be tested separately by the laboratory.*
5. *Except for officially recognized combined therapies which have compendia methods of analysis, all other products containing more than one active ingredient shall be treated as if each active ingredient is a separate sample. In such a case, the importer shall be required to pay for the analysis of each active ingredient.*
6. *For MA (pre-market) samples, they must be accompanied with the relevant documents (certificates of analysis - CoAs, quotations from LMHRA's Department of Evaluation & Registration, invoices/receipts from the Finance Department, sample collection and results*

due-date forms from the Inspectorate Department, etc.). COAs and all relevant documents MUST be submitted in their original copies.

7. *Any COA submitted with an in-house method of analysis MUST be accompanied with an analytical method validation protocol and report in their original copies. Original signed copies may be scanned. All components of the original validation document MUST be scanned.*
8. *The time of submission of MA samples shall be no later than 12 noon; MA samples submitted after 12 noon shall be deemed submitted the following day.*
9. *Samples shall be submitted directly to the Quality Control Section of the QC Lab and received by a designated staff in the Sample Registry Unit which is a part of the Quality Control Section.*
10. *The QC Lab shall not accept any product for which a barcode is used as a substitute for manufacturer's information, manufacturing date and expiry date. In line with the new organogram of the Lab*
11. *Biological samples must be kept under cold chain before and during submission to the QC Lab.*

Any sample which is not submitted in line with the above requirements shall either be quarantined in the QC Lab pending the submission of the deficit requirement(s) or be rejected.

The conditions for samples to be quarantined are as follows:

- CoAs for samples received for which the authenticity is doubtful. In such a case, the customer shall be notified of the deficiency(ies) and requested to correct said deficiency(ies) within seven (7) working days for market authorization and fourteen (14) working days for registration.
- The MA samples are not accompanied with their CoAs.
- No validation protocol and report are presented for a sample with an in-house method of analysis as indicated in the CoA;

The conditions for samples to be rejected are as follows:

- If sample is received with evident seal broken.
- If the sample shows deterioration (leakage of the package, caked sample, etc.).

1.5. Release of Results from Analysis

The release of results of analysis by the QC Lab shall be guided by the following requirements:

- *Results of analysis shall be released only to the QC Laboratory's customer (the LMHRA's Inspectorate Department).*
- *The representative of the customer shall sign for the results of analysis he/she receives.*
- *The customer must ensure that each CoA and the covering letter received are signed and stamped, and bear the full address and logo of the QC Lab to prove validity.*
- *The results of analysis shall be released within the specified period – seven (7) working days for fast track and 21 working days for regular MA samples. For PMS samples, the duration*

of testing shall be mutually determined by the QC Lab and the LMHRA Department which has submitted the samples.

- *Duration of testing for registration samples is indicated in Section 1.1 of this guideline.*

1.6. Documentations for Submission by the Importer

The following shall constitute the documents to be submitted and the appropriate contents of said documents:

Certificate of Analysis

WHO has recommended a model certificate of analysis (CoA) for use in trade by manufacturers of pharmaceutical substances, excipients and medicinal products. A model of such a certificate is shown in the Appendix. The items included are based on good practices for national pharmaceutical control laboratories and good manufacturing practices (GMP) for pharmaceutical products. The certificate lists the results and includes a final evaluation and the conclusions of the examination of one or more samples.

Therefore, all CoAs presented to the QC Lab of LMHRA must conform to the WHO model CoA (see *Appendix*). The CoAs must be originals (not copies or duplicates) or their authenticity must otherwise be assured, i.e., they must be issued by the manufacturer of the product or the contracted laboratory which tested the product. The CoA must also be based on the analytical worksheet of the laboratory testing the sample(s). The CoA should include:

- The name and address of the laboratory performing the tests.
- Product name (generic and/or brand) along with the strength (concentration)
- Batch/lot number
- Specification and method used
- The registration number of the certificate of analysis.
- The name, description (i.e., grade, quantity received, type of container) and number (used by the original manufacturer and re-packer/trader) of the batch for which the certificate is issued, the date of manufacture, and the expiry date (or retest date).
- The date on which the batch for which the certificate is issued was received.
- A reference to the test procedure used, including the acceptance criteria (limits).
- The results of all tests performed on the batch for which the certificate is issued (in numerical form, where applicable) and a comparison with the established acceptance criteria (limits).
- A statement indicating whether the results were found to comply with the requirements.
- The date(s) on which the test(s) was (were) performed.
- The signatures of all authorized persons.
- The name, address, and telephone/number of the original manufacturer. If supplied by re-packers or traders, the certificate should show the name, address, and telephone and fax numbers of the re-packer/trader and a reference to the original manufacturer.

- A statement of the expected conditions of shipping, packaging, storage and distribution, deviation from which would invalidate the certificate.
- A copy of the certificate generated by the original manufacturer, if the sample is supplied by a re-packer or trader.

Analytical Method Validation Protocol and Report

It is a good manufacturing practice for pharmaceutical manufacturers to ensure that their finished products meet the required standards. Quality control testing of finished products must comply with internationally accepted standards such as the United States Pharmacopoeia (USP), British Pharmacopoeia (BP), International Pharmacopoeia (Int. Ph.), European Pharmacopoeia (Eur. Ph.), Indian Pharmacopoeia (IP), etc. Non-standard (in-house) methods used for analysis of finished products must be validated in line with the ***International Conference on Harmonization (ICH) Guideline on Validation of Analytical Procedures: Text and Methodology Q2(R1) of November 2005***.

Method Validation is an established documented evidence that provides a high degree of assurance that a specific method, and the ancillary instruments included in the method, will consistently yield results that accurately reflect the quality characteristics of the product tested. Method validation is an important requirement for any package of information submitted to LMHRA in support of new product marketing or clinical trials applications. The analytical method development and validation play significant roles in the drug discovery, development, manufacture of pharmaceuticals and estimation of small molecules. The official test methods that result from these processes are used by quality control laboratories to ensure the accuracy, precision, selectivity, sensitivity, reproducibility, stability, and performance of drug products.

The **Protocol of analysis** must be in a standard format that contains information as stated below:

- Product name
- Batch/lot number
- Name and address of manufacturer
- Name, signature and designation of authorized person
- Effective date
- Review date

Protocol of analysis must consist of all test methods and specifications that are carried out by the manufacturer. Standard pharmacopoeias, for example, BP/USP can be used as references. The tests and specifications in the pharmacopeias are the minimum requirements.

Photocopies of methods directly copied from pharmacopoeias are not acceptable.

Manufacturers may use methods from those standard references but must have their own written and detailed procedure.

Manufacturers must confirm that all test methods in their protocol of analysis perform as expected.

Copies of chromatograms (HPLC/GC/TLC), UV spectrum etc. must be submitted together with the protocol of analysis.

Protocol of analysis must be properly ordered with proper numbering for all tests and specifications.

All references stated in the protocol of analysis must be submitted and clearly labeled.

Protocol of analysis submitted must be in English. Protocol of analysis in other languages will be rejected if the English interpretation is not included.

An authorized copy of latest certificate of analysis for the product concerned must be submitted with the protocol of analysis.

Validation Report: The most widely applied typical validation characteristics for various types of tests are:

a. Accuracy
b. Precision (repeatability and intermediate precision)
c. Specificity
d. Detection limit
e. Quantitation limit
f. Linearity
g. Range
h. Robustness
i. System Suitability

In addition, method validation information should also include stability of analytical solutions, appendices and references.

CHAPTER 2: QUALITY ASSURANCE/QUALITY CONTROL OF HERBAL MEDICINES

2.1. General

Over the years, there has been a constant, and at times, exponential growth in global interest in the use of herbal medicines. This increase in popularity and usage of herbal medicines is evident in the global market. Herbal medicines, including finished herbal products and the starting materials for their production, such as medicinal plants, herbal materials, herbal preparations and herbal dosage forms, are moving into international commerce and global trade, which reflects their increased economic value and importance.

Some degree of quality control should exist, regardless of the form of herbal preparation. Without proper quality control, there is no assurance that the herb contained in the package is the same as what is stated on the outside label. A number of factors such as climate, soil nutrients and pH, plant collection time, plant organs and post-harvesting factors may affect the safety, efficacy and quality of any herbal drug.

WHO in its volume, *Quality Control Methods for Medicinal Plant Materials*, listed several parameters which are valuable in assessing the quality of plant drugs. These include, *visual inspection, identification, sensory characters, macro- and microscopic characters, moisture content, ash values, extractive values, volatile matter, microbial load, fingerprint by TLC, heavy metals, pesticide residues* and *radioactive contaminants*. Also depending on the nature of the herbal product, one or more determinations for *bitter value, tanning test, foaming, hemolytic* and *swelling indices* can be made.

With the above-mentioned considerations, herbal medicines cannot be excluded when describing quality-related issues.

2.2. Submission of Herbal Medicines for Pre-Registration Testing

As it is for allopathic medicines, quality assurance of herbal products at LMHRA begins with the submission of product dossiers to the Evaluation and Registration department. The submission of dossiers is accompanied with the submission of the relevant product by the manufacturer.

The requirements for the submission of herbal medicines to the Evaluation and Registration Department for onward submission to the QC Lab of LMHRA are similar to those for allopathic medicines as defined in Section 1.1 of this guideline.

The durations of testing as well as the penalty for non-compliance are the same as those for the allopathic medicines as contained in Section 1.1 of this guideline.

2.3. Sampling of Herbal Medicines for MA and PMS

The sampling methodology for herbal medicines for MA and PMS is the same as that for allopathic medicines as contained in Section 1.2 of this guideline.

The appropriate sample scheduled must be observed during the sampling exercise. For MA, the importer must provide adequate samples as spelled out in the sample schedule without any charge/cost to the sampling team. For PMS, the sampling team shall procure the required quantities of samples from the importer/entity consistent with the price tag on each sample in the store.

2.4. Sample Schedule

MA and PMS of herbal medicines have the same sample schedule as it is for allopathic medicines. Also, the sample schedule for registration of herbal medicines is the same as that for allopathic medicines. Customers are required to check with the Department of Evaluation and Registration for information about the sample schedule released by the QC Laboratory for MA & PMS, and that for registration of herbal medicines.

2.5. Submission and Receipt of Herbal Medicine Samples

The submission to and receipt of samples of herbal medicines by the QC Lab shall be guided by the same requirements for allopathic medicines as contained in Section 1.4 of this guideline.

The conditions for the QC Lab to quarantine or reject herbal medicine samples are similar to those for allopathic medicines as contained in Section 1.4 of this guideline.

2.6. Release of Analytical Test Results for Herbal Medicines from the QC Laboratory

The release of results of analysis of herbal medicines by the QC Lab shall be guided by the same requirements for allopathic medicines as contained in Section 1.5 of this guideline.

2.7. Documentations for Submission by the Importer – herbal Medicines

The following shall constitute the documents to be submitted and the appropriate contents of said documents for herbal medicines:

Certificate of Analysis

The WHO recommended model certificate of analysis (see *Appendix*) is also useful for herbal products. As it is for allopathic medicines, certificates of analysis must be originals (not copies or duplicates) or their authenticity must otherwise be assured, i.e., they must be issued by the supplier of the material concerned (manufacturer, broker, etc.), or based on the analytical worksheet of the laboratory testing the sample(s). The certificate should include:

- Product name
- Batch/lot number

- Name and address of manufacturer
- Quantitative list of ingredients along with their respective strengths/concentrations; if this is difficult, it could be replaced by the plant names and plant parts used (i.e., Latin name);
- The registration number of the certificate of analysis.
- The name and address of the laboratory performing the tests.
- The name, description (i.e., grade, quantity received, type of container) and number (used by the original manufacturer and re-packer/trader) of the batch for which the certificate is issued, the date of manufacture, and the expiry date (or retest date).
- The date on which the batch for which the certificate is issued was received.
- A reference to the test procedure used, including the acceptance criteria (limits).
- The results of all tests performed on the batch for which the certificate is issued (in numerical form, where applicable) and a comparison with the established acceptance criteria (limits).
- A statement indicating whether the results were found to comply with the requirements.
- The date(s) on which the test(s) was (were) performed.
- The signatures of all authorized persons (the analysts who performed the test/s, the Quality Assurance and/or Quality Control Manager and the Director/Head of the Laboratory or an authorized person).
- The name, address, and telephone and fax numbers of the original manufacturer. If supplied by re-packers or traders, the certificate should show the name, address, telephone and fax numbers of the re-packer/trader and a reference to the original manufacturer.
- A statement of the expected conditions of shipping, packaging, storage and distribution, deviation from which would invalidate the certificate.
- A copy of the certificate generated by the original manufacturer, if the sample is supplied by a re-packer or trader.

Analytical Method Validation Protocol and Report

Most herbal medicines are quality controlled through manufacturer's in-house methods of testing. Hence, these non-standard analytical methods must be validated.

The contents of the analytical method validation protocol and report for herbal medicines are similar to those for allopathic medicines as contained in Section 2.6 of this guideline.

CHAPTER 3 CHALLENGING RESULTS FROM LABORATORY TESTING

The QC Laboratory of LMHRA reposes high confidence in the competence of laboratory personnel who conduct product analysis/testing. Therefore, with a high degree of accuracy, the analytical test results issued are credible. Additionally, in keeping with quality assurance procedures, non-conforming and out-of-specification results are always investigated by the Quality Assurance Section of the QC Lab in collaboration with the Quality Control Section to validate and assure the quality of such test results.

Notwithstanding, the right of the customer to challenge the results of any laboratory analysis is guaranteed. In so doing, a customer wishing to challenge any analytical test results released by the QC Lab may do so under the following conditions:

- Send a communication challenging the test report to the Managing Director of LMHRA;
- Attend a hearing to be presided by the LMHRA Hearing Board
- If not satisfied from the hearing, the customer may request a verification test. This shall be performed by a 3rd-party laboratory which is ISO 17025 accredited and has a contract with LMHRA.
- The cost of testing at the 3rd–party laboratory shall be borne by the customer.
- Upon payment of the testing fee by the customer, the QC Lab along with a representative of the customer shall proceed to jointly package and ship the test items to the 3rd-party laboratory. Test item(s) shall be collected and packaged **only** from the remainder of the same batch. The cost of shipment/courier shall also be borne by the customer.
- When the results are released by the 3rd-party laboratory, the QC Lab shall share with the customer.
- The result from this ISO accredited laboratory shall be deemed final and the appropriate action shall be taken based on this test result. The sample/product shall be released from quarantine if the test result from the accredited 3rd-party lab contradicts that of the LMHRA QC Lab. If the two results corroborate, the appropriate regulatory action shall be taken.

CHAPTER 4: SAFETY CONSIDERATIONS

4.1 Packaging and Labeling

4.1.1 General Considerations

Packaging may be defined as the collection of different components (e.g., bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use. Packaging preserves the stability and quality of medicinal products and protects them against all forms of spoilage and tampering. It is possible for the package to interact with the product due to the combination of a multiplicity of container components and active pharmaceutical ingredients, excipients and solvents used in a variety of dosage forms.

Hence, medicinal products need to be protected; packaging needs to be done in containers that conform to prescribed standards, particularly with respect to the exclusion of moisture and light and the prevention of leaching of extractable substances into the contents and of chemical interaction with the contents.

The quality of the packaging of pharmaceutical products plays a very important role in the quality of such products. It must:

- protect against all adverse external influences that can alter the properties of the product, e.g., moisture, light, oxygen and temperature variations;
- protect against biological contamination;
- protect against physical damage;
- carry the correct information and identification of the product.

Packaging has the following functions:

- **Containment –** high-quality packaging of the medicinal product requires that the package be prevented from leakage, the product be prevented from diffusion and permeation into the package, the package be strong enough to hold the contents when subjected to normal handling, and that the package should not be altered by the ingredients of the formulation in its final dosage form.
- **Protection** - the product must be protected against all adverse external influences such as light, moisture, oxygen, biological contamination or mechanical damage, that may affect its quality or potency.
- **Stability** - the primary package, which directly holds the medicinal product must show stability and compatibility throughout the shelf-life of such product.
- **Storage** – packaging materials must conform to the storage conditions and storage areas of the product.

Labeling is the use of a label to identify a medicinal product and explain what such product does. Throughout manufacturing, a succession of specific outer labels is applied to the container of the medicinal product. WHO guidelines on GMP for pharmaceutical products give specifications for labels to be used for finished drug products.

Written labels on the packaging:

- permit the identification of each active ingredient by means of its INN;
- give the dosage form and the trade name/trademark;
- give all information concerning the medicinal product, as required by national legislation, must be stated on the packaging;
- preserve the stability of the medicinal product by giving advice on its storage;
- permit the follow-up of a specific medicinal product by means of the batch number on the labels.

Packaging and labelling may help to reinforce the instructions given by the physician or the pharmacist, and improve compliance with drug therapy. In this respect, packaging becomes a compliance aid. If the patient feels at ease with the packaging and route of administration, the design of the packaging may become a key factor in increasing compliance.

Given the link between the quality of a pharmaceutical product and the quality of its packaging and labeling, pharmaceutical labeling and packaging materials and systems must be subject, in principle, to the same quality assurance requirements as pharmaceutical products. Quality assurance requirements follow the WHO guidelines for good manufacturing practices (GMP). Bad packaging which is the result of deficiencies in the quality assurance system for packaging can have serious consequences, and packaging defects can create problems that may result in drug recalls. Such defects may include breakage, and problems relating to printing or inks, or errors on labels and package inserts (patient information leaflets).

4.1.2 Specific packaging and labeling requirements at LMHRA QC Lab

Pursuant to the WHO guidelines for labeling and packaging, and in consideration of peculiar circumstances in Liberia, all allopathic medicinal products must at all times comply with the following requirements:

1. The primary package (which directly holds the medicinal product) shall be such that the integrity of the product is maintained, protecting the product against moisture, light, oxygen, temperature variations, biological contamination and physical damage;
2. The medicinal product shall be accepted/received only if it is contained in both the primary and at least the secondary package;
3. The closure of any of the packages must maintain the tamper-evident seal;
4. All packages of the product must be correctly labeled and there must be a uniformity of the label on all packages of the product;
5. On visual inspection, solutions, reconstituted solutions and intravenous infusions (except dispersions) should be clear and free from visible particulate matter.
6. The label must be legible at all times during the shelf-life of the product;
7. The label must be written **only** in English language; however, if written in a foreign language, the English interpretation must be clearly stated;
8. Printed labels should be indelible at all times during the shelf-life of the product;
9. Stamped and over-printed labels shall not be accepted; embossed and engraved labels must be readable;
10. The label **must** contain the following on all packages:

    - official product name;
    - active and inactive ingredients (inactive ingredients are optional);

- strength/concentration of each active & inactive ingredient, and the method of analysis of each;
- purpose and use;
- lot/batch number;
- directions for use;
- manufacturer's name and complete address; (**Note:** If the label reads "**manufactured for**" instead of "**manufactured by**", it does not indicate the actual manufacturer; also, if the exact address, including the country in which the product is manufactured is not indicated, it is **UNACCEPTABLE**.); if the manufacturer is different from the packager, the label must also include the full address of the packager/re-packager. Similarly, if the testing laboratory for the finished product is a contracted laboratory, then the full address of that laboratory must also be included on the label.
- manufacturing and expiry dates (**expiry date is mandatory**);
- any special storage conditions required for the product;
- after the stability of the product has been evaluated, one of the following recommendations as to storage conditions can be prominently indicated on the label:
  (i) store under normal storage conditions;
  (ii) store between 2 and 8°C (under refrigeration, no freezing);
  (iii) store below 8°C (under refrigeration);
  (iv) store between -5 and -20°C (in a freezer);
  (v) store below -18°C (in a deep freezer).

11. For herbal medicines, the label should include the following:

- brand name of product;
- quantitative list of ingredients; if this is difficult, it could be replaced by the plant names and plant parts used (i.e. Latin name);
- strength and method of analysis of each ingredient;
- dosage form and dosage;
- mode of administration;
- duration of use;
- lot/batch number;
- manufacturer's complete address;
- manufacturing and expiry dates;
- indications; contraindications, warnings, precautions and major drug interactions, if possible;
- adverse effects, if any;
- storage condition(s);
- warnings;
- allergic reactions (if any).

Sanctions: If a product brought to the QC Lab is observed to have compromised packaging which affects the integrity of such sample, it shall be rejected.

If there is a deficiency in any of the labeling requirements, the product shall be accepted, but shall be subjected to quality evaluation/testing.

4.2 Handling and Transportation

Drug products must be transported in a manner that ensures the products will be maintained within an acceptable temperature range as defined in the approved labelling and supported by stability data. Temperature excursions outside of their respective labelled storage conditions, for brief periods, may be acceptable provided stability data and scientific/technical justification exist demonstrating that product quality is not affected.

Any controlled transport and/or storage conditions as well as warning statements (for example, "Time and Temperature Sensitive", "Do Not Freeze") must be clearly stated on the label applied to shipping containers. This label should be securely affixed and indelible. The label and shipping documents must clearly state that these products should be transferred without delay to the specified storage temperature upon receipt.

The transport process and containers should be designed to prevent damage and maintain the integrity and quality of the drug products. For example, transport conditions for ampoules should limit their exposure to physical stress to avoid the development of hairline cracks.

Where controlled storage conditions (for example, temperature, relative humidity, light, etc.) are required during transit, the necessary environmental controls must be in place.

Within a transportation container, the packaging configuration, which provides the primary means of environmental control for the drug product, should ensure that the drug product remains within the acceptable temperature range.

Refrigerated vehicles/transportation containers should be mapped and monitored, if they provide the primary means for environmental control. However, this may not be necessary if a qualified insulated container/package, or an appropriate temperature monitoring device on the package or selected packages, or gel packs or similar approved means, or lane profile data are used as the primary means of environmental control.

Vehicles and equipment used to distribute, store, or handle drugs should be suitable for their use and appropriately protective of the products to prevent exposure to conditions that could affect their stability and packaging integrity, as well as prevent contamination of any kind.

Loading activities (loading and unloading) should be done in a manner that preserves the quality of the drugs.

The use of dry ice in the transportation of drugs must not adversely affect the drug product or the primary package and must be handled appropriately.

Where controlled conditions (for example, temperature, relative humidity, light, etc.) are required during transit, the recipient should examine the shipment upon reception, following written procedures, to ensure the conditions have been met and record the results.

Products must be promptly transferred to the appropriate, environmentally controlled storage area.

Sanctions: Products for which handling and transportation requirements are compromised shall be rejected by the QC Lab.

4.3 Storage

All medicines should be stored according to the conditions described on the label. When specified on the label, controls for humidity, light, etc., should be in place. Storage areas should be designed or adapted to ensure good storage conditions.

Storage areas should be clean, dry, and have adequate circulation. It should be maintained within acceptable temperature limits. To reduce human error, general storage areas must be well lit.

Adherence to these conditions should be checked, monitored and recorded. Temperatures should be controlled and monitored using calibrated monitoring devices and records of temperature and alarms, where applicable, should be maintained. Monitoring of storage facilities is conducted at points representing the worst-case scenarios of the temperature range based on temperature mapping.

Refrigerators and freezers used to store medicines should be well maintained, equipped with alarms, free from excessive frost buildup, a two-door unit with separate freezer compartment and door when the freezer and refrigerator are combined, allow for adequate air distribution and orderly storage within the chamber, have sensors for continuous monitoring and alarms located at the points representing the temperature worst-case scenarios, calibrated as required by the calibration program, equipped with a backup power source or have alternate storage available in the event of a power failure for critical refrigeration equipment, including both walk-in and stand-alone refrigerators/freezers or warehouses, and of commercial grade and not be of household type, unless they incorporate the above controls. The use of household type refrigerators and freezers is discouraged.

4.4 Package Inserts

Each product package ***must*** contain a package insert written in English.

A package insert is a document included in the package of a medication that provides information about that drug and its use. For prescription medications, the insert is technical, providing information for medical professionals about how to prescribe the drug. Package inserts for prescription drugs often include a separate document called a "patient package insert" with information written in plain language intended for the end-user -- the person who will take the drug or give the drug to another person, such as a minor. Inserts for over-the-counter medications are also written plainly.

The package insert includes details and directions that health care providers need to prescribe a drug properly, including approved uses for the drug, contraindications, potential adverse reactions, available formulations and dosage, and how to administer the drug. An exception to this is the case of infusions which are not packaged with inserts.

Without a package insert, the product shall be rejected by the QC Lab.

Document History

Summary of Revision	Rationale for Revision
Rev 01	
New Edition	

APPENDIX: WHO MODEL CERTIFICATE OF ANALYSIS

Registration number of sample or certificate: _____

Name and address of laboratory testing the sample:

_____

_____

_____

Sample information

Name of product (INN, brand name(s), etc.):

_____

Dosage form (if applicable):

_____

_____

Marketing authorization number (if applicable):

_____

Description (appearance of container and contents):

_____

_____

Batch number(s):

_____

Required storage conditions:

_____

Date received: _____ Date of manufacture: _____

Expiry date (for medicinal products) or retest date (for starting materials or excipients):

_____

Name and address of original manufacturer:

_____

_____

_____

Telephone: _____ Fax: _____

Name and address of repacked and/or trader (if applicable): _____

Telephone: _____ Fax: _____

Test procedure (reference to test procedure) (if applicable)	Result (numerical result) (if applicable)	Acceptance criteria (limits)
_____	_____	_____

A. Tests performed on samples from batch for which certificate is issued

B. Tests performed as part of periodic statistically based testing program

_____

Conclusions: _____

_____

_____

Compliance with acceptance criteria: yes ☐ ☐ no

Date test performed/finalized: _____

Name and address of head of laboratory/authorized person:

_____

_____

Telephone: _____ Fax: _____

Signatures:_____