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**NATIONAL AGENCY FOR FOOD & DRUG ADMINISTRATION &
CONTROL (NAFDAC)**

**GUIDELINES FOR CONTRACT
MANUFACTURING OF FINISHED
PHARMACEUTICAL PRODUCTS IN NIGERIA**

Drug Evaluation & Research (DER) Directorate

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Effective Date: 3rd February, 2021

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1. GENERAL

- 1.1 These guidelines are for the interest of the general public and in particular organizations intending to manufacture finished pharmaceutical products using contract manufacturing arrangements in Nigeria.
- 1.2 It is necessary to emphasize that, no regulated product should be manufactured, imported, exported, advertised, sold or distributed in Nigeria unless it has been registered in accordance with the provisions of the Food, Drugs and Related Products Act Cap F33 LFN 2004 (formerly decree 19 of 1993) and the accompanying guidelines.
- 1.3 A drug product should not be manufactured in Nigeria unless the facility has been inspected, found to comply with Good Manufacturing Practices and an Authority to Manufacture pharmaceutical products is issued by NAFDAC.
- 1.4 These guidelines prescribe the minimum requirements to be met by parties wishing to engage in contract manufacturing of pharmaceutical products i.e. human and veterinary medicines, biologics, herbal medicines and nutraceuticals; as well as medical devices.

2. DEFINITIONS

- 2.1 **Contract Facility:** a site where one or more manufacturing operations take place on behalf of the Contract Giver.
- 2.2 **Contract Giver:** a legal entity who has legal ownership of the finished product and who will be applying to the Agency for Marketing Authorization or entity that orders the conduct of a component of manufacturing to be carried out on their behalf by another entity.
- 2.3 **Contract Manufacturer/Contract Acceptor:** an entity that engages in GMP activities, including implementation of oversight and controls over the manufacture of drugs to ensure quality on behalf of other parties.
- 2.4 **Contract Manufacturing:** manufacturing by Contract Manufacturer/Contract acceptor on behalf of the Contract giver.
- 2.5 **Good Manufacturing Practice (GMP):** that part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by their marketing authorisations. It ensures that pharmaceutical products are manufactured so that they do not place the populace at risk.
- 2.6 **Manufacturing:** includes processing, packaging, holding, labeling operations, testing, and quality unit operations.
- 2.7 **Manufacturer:** an entity that engages in GMP activities, including implementation of oversight and controls over the manufacture of drugs to ensure quality.

Effective Date: 3rd February, 2021

Review Date: 2nd February, 2026

2.8 **Quality Agreement:** a comprehensive written agreement between parties involved in the contract manufacturing of pharmaceutical products that defines and establishes each party's manufacturing activities in terms of how each will comply with GMP. Quality agreements should not cover general business terms and conditions such as confidentiality, pricing or cost issues, delivery terms, or limits on liability or damages. Quality agreements may be reviewed during inspections.

3. PRINCIPLES GUIDING CONTRACT MANUFACTURING ARRANGEMENTS

3.1 A manufacturer may perform all operations and activities or may engage an outside party or parties to perform some or all of the operations and activities under contract. NAFDAC shall allow product owners/manufacturers to contract some of these operations to any Contract Facility as defined above.

3.2 Contract production and any other activity covered by GMP that is outsourced must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product, or work or analysis, of unsatisfactory quality.

3.3 All arrangements for contract manufacturing including technology transfer and any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

3.4 Contract manufacturing may be undertaken only by a manufacturer who holds a valid manufacturing authorization.

3.5 Contract manufacturers may perform a variety of manufacturing operations and activities, including but not limited to:

3.5.1 Product formulation

3.5.2 Tableting/Encapsulation

3.5.3 Fill and finish

3.5.4 Primary/secondary packaging and labeling

3.5.5 Sterilization

3.5.6 Stability studies

3.5.7 Analytical testing and other laboratory services

3.6 Finished pharmaceutical products that are not manufactured in compliance with GMP requirements are considered to be adulterated.

4. TYPES OF CONTRACT FACILITIES

4.1 The Agency has classified contract manufacturing facilities into two (2) groups for proper definition of the scope of operations and effective regulation as follows:

4.1.1 **Full Contract Manufacturing Facilities (FCMF)** – These are establishments that do not have any product registered by the Agency and are only involved in contract manufacturing operations for other parties.

Effective Date: 3rd February, 2021

Review Date: 2nd February, 2026

- 4.1.2 **Partial Contract Manufacturing Facilities (PCMF)** – These are establishments that are holders of Market Authorization issued by NAFDAC for manufactured products and are also involved in commercial contract manufacturing operations for other parties.

5. RESPONSIBILITIES OF PARTIES INVOLVED IN CONTRACT MANUFACTURING

- 5.1 Each party engaged in the manufacture of a drug is responsible for ensuring compliance with GMP for the manufacturing activities it performs.
- 5.2 For both product owners and contract facilities that conduct manufacturing operations, GMP “includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.
- 5.3 The responsible person designated by the Contract Giver should be party to approving or rejecting pharmaceutical products manufactured by the Contract Facility, including final release except if such responsibility is otherwise established in the Quality Agreement.

6. RESPONSIBILITIES OF THE CONTRACT GIVER

- 6.1 The Pharmaceutical Quality System (PQS) of the contract giver should include the control and review of any outsourced activities. The contract giver is responsible for:
- 6.1.1 Assessing the legality, suitability and competence of the contract acceptor to successfully carry out the work or tests required
- 6.1.2 Approval for contract activities and;
- 6.1.3 Ensuring by means of the contract that the principles of GMP incorporating QRM principles are followed to include the implementation of oversight and controls over the manufacture of pharmaceuticals to ensure quality and management of risk.
- 6.2 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements.
- 6.3 The contract giver should ensure that the contract acceptor is fully aware of any hazards associated with the product, work or tests that might pose a risk to premises, equipment, personnel, other materials or other products.
- 6.4 The contract giver should review and assess the records and results related to the outsourced activities.
- 6.5 The contract giver should ensure that all products and materials delivered by the contract acceptor have been processed in accordance with GMP and the marketing authorization; comply with their specifications and that the product has been released by the authorized person in accordance with GMP and the marketing authorization.
- 6.6 The contract giver should monitor and review the performance of the contract acceptor including the implementation of any needed improvements and their effectiveness.

Effective Date: 3rd February, 2021

Review Date: 2nd February, 2026

6.7 The contract giver is responsible for ensuring that the contract acceptor understands that his or her facilities and activities will be subject to inspection by competent authorities.

7. RESPONSIBILITIES OF THE CONTRACT MANUFACTURER/ACCEPTOR

7.1 The contract acceptor must have adequate premises, equipment, knowledge, experience and competent personnel to satisfactorily carry out the work ordered by the contract giver.

7.2 The contract acceptor should ensure that all products or materials delivered to the facility are suitable for manufacturing of finished pharmaceutical products.

7.3 The contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements.

7.4 Arrangements made between the contract acceptor and any third party should ensure that information and knowledge, including that from assessments of the suitability of the third party, are made available in the same way as between the original contract giver and contract acceptor.

7.5 The contract acceptor should refrain from any activity (including unauthorized changes outside the terms of the contract) that may adversely affect the quality of the product manufactured for the contract giver.

8. THE CONTRACT

8.1 There must be a written contract between the contract giver and the contract acceptor which clearly establishes the responsibilities of each party, covering the outsourced activities, the products or operations to which they are related, communication processes relating to the outsourced activities and any technical arrangements made in connection with it.

8.2 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

8.3 Technical aspects of the contract (the Quality Agreement) should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP. The Quality Agreement should be a separate document, or at least severable, from the commercial contract.

8.4 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

8.5 The contract should clearly describe who is responsible for contracted activities, e.g. knowledge management, technology transfer, supply chain, subcontracting, testing and releasing materials and undertaking production and QC, including in-process controls, and who has responsibility for sampling and analysis.

Effective Date: 3rd February, 2021

Review Date: 2nd February, 2026

8.6 Manufacturing, analytical, distribution records and reference samples should be kept by, or be available to, the contract giver.

8.7 Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect, or to investigating in the case of a suspected falsified product or laboratory fraud, must be accessible and specified in the defect/recall procedures of the contract giver.

8.8 The contract must state that the Contract Giver and the Agency have the right to inspect the facilities of the contract acceptor.

8.9 The contract should describe the handling of starting materials, intermediate and bulk products; and finished products if they are rejected.

9. DOCUMENTING GMP ACTIVITIES IN QUALITY AGREEMENTS

9.1 A quality agreement describes the Contract Giver's and the Contract Acceptor's roles and manufacturing activities under GMP.

9.2 A well-written quality agreement should use clear language, define key manufacturing roles and responsibilities and establish expectations for communication and providing key contacts for both parties.

9.3 It will specify which products and/or services the Contract Giver expects from the Contract Acceptor and who has final approval for various activities.

9.4 Most quality agreements contain the following sections:

9.4.1 Purpose/Scope— to cover the nature of the contract manufacturing services to be provided.

9.4.2 Definitions — to ensure that the Contract Giver and Contract Acceptor agree on precise meaning of terms in the quality agreement.

9.4.3 Resolution of disagreements — to explain how the parties will resolve disagreements about product quality issues or other problems.

9.4.4 Manufacturing activities — to document quality unit and other activities associated with manufacturing processes as well as control of changes to manufacturing processes.

9.4.5 Life cycle of, and revisions to, the quality agreement.

9.5 Quality agreements should state that manufacturing services provided by contract facilities will comply with GMP.

9.6 Manufacturing activities are the most important element in a quality agreement and the most critical pieces are quality and change control, as described in the following sections:

9.7 Quality Unit Activities

9.7.1 This section of a quality agreement addresses each party's quality unit activities and should define in detail how the parties will work together to ensure that products are manufactured in compliance with GMP. Note that assigning quality control or other

Effective Date: 3rd February, 2021

Review Date: 2nd February, 2026

- activities to either the Contract Giver or Contract Facility in the quality agreement does not relieve either party from compliance with applicable GMP requirements.
- 9.7.2 The section should be clear with respect to product release. Contract facilities are responsible for approving or rejecting the product or results of their manufacturing operations (e.g., test results, finished dosage forms, or in-process materials) while the Contract Giver is ultimately responsible for releasing or rejecting drug products manufactured by the Contract Facility irrespective of any delegation of powers in this regard that may be so established in the agreement.
- 9.7.3 The agreement should describe how and when the Contract Giver and the Contract Acceptor will communicate with each other, both verbally and in writing and this includes identifying appropriate contact personnel within the Contract Giver's and Contract Acceptor's organization.
- 9.7.4 This section of the agreement should also cover audits, inspections, and communication of findings. The agreement should allow the Contract Giver and NAFDAC to evaluate and audit contract facilities to ensure GMP compliance for specific operations. This provision should cover both routine quality audits and for-cause inspections.
- 9.7.5 The Quality Agreement should address when, how, and what information the Contractor will report to Contract Giver about objectionable conditions observed during inspections and audits of the Contract Facility.

9.8 Facilities and Equipment

- 9.8.1 This section of a quality agreement should identify the specific site(s) where the Contract Acceptor will perform manufacturing operations, including the address of and specific services to be provided at each site.
- 9.8.2 The agreement should indicate which party will be validating processes and qualifying and maintaining equipment and applicable systems relevant to the contracted operations. These include information technology and automated control systems, environmental monitoring and room classification, utilities, and any other equipment and facilities that must be maintained to perform the contracted manufacturing operations in compliance with GMP.
- 9.8.3 The agreement also should identify which party will approve equipment validation, qualification, and maintenance activities.
- 9.8.4 The agreement should indicate how the parties will communicate information about preventing cross-contamination and maintaining traceability when a Contract Acceptor processes drugs for multiple organizations.

Effective Date: 3rd February, 2021

Review Date: 2nd February, 2026

9.9 Materials Management

- 9.9.1 This section of a quality agreement should indicate which party will establish specifications for materials as well as which party will establish processes for auditing, qualifying, and monitoring material suppliers.
- 9.9.2 The agreement should also identify which party will conduct required sampling and testing in compliance with GMP.
- 9.9.3 This section of the quality agreement should address how the parties will ensure appropriate inventory management, including labeling, label printing, inventory reconciliation, and product status identification (e.g., quarantine).
- 9.9.4 The agreement should address how the Contract Facility will prevent mix-ups and cross-contamination.
- 9.9.5 The agreement should define responsibility for physical control of materials at different points in the manufacturing process e.g. the quality agreement should cover responsibilities for proper conditions for storing and transporting or shipping of materials and each party's roles in storage and transport of finished products.

9.10 Product-Specific Considerations

- 9.10.1 A comprehensive quality agreement may address specific considerations related to individual products such as the parties' expectations of each other regarding:
- a. Product/component specifications
 - b. Defined manufacturing operations, including batch numbering processes
 - c. Responsibilities for expiration/retest dating, storage and shipment, and lot disposition
 - d. Responsibilities for process validation, including design, qualification, and ongoing verification and monitoring
 - e. Provisions to allow the Contract Giver's personnel access to the Contract Facility when appropriate.
- 9.10.2 The quality agreement should indicate how the Contract Giver will transfer knowledge, such as product and process development information, to the Contract Acceptor to ensure the product will be manufactured in compliance with GMP, and conversely how the Contract Acceptor should share with product quality information gained throughout the product life cycle with the Contract Giver.

9.11 Laboratory Controls

- 9.11.1 This section of the agreement should by define roles and responsibilities of each party for laboratory controls especially in the following areas:
- a. Procedures delineating controls over sampling and testing of samples
 - b. Protocols and procedures for communicating all laboratory test results conducted by the Contract Facility to the Contract Giver for evaluation and consideration in final product disposition decisions.

Effective Date: 3rd February, 2021

Review Date: 2nd February, 2026

- c. Routine auditing procedures to ensure that a contract facility's laboratory equipment is qualified, calibrated, and maintained in a controlled state in accordance with GMP.
- d. Designation of responsibility for investigating deviations, discrepancies, failures, out-of-specification results etc.

9.12 Documentation

- 9.12.1 The quality agreement should define expectations between the Contract Acceptor and the Contract Giver to review and approve documents. It should also describe how changes may be made to standard operating procedures, manufacturing records, specifications, laboratory records, validation documentation, investigation records, annual reports, and other documents related to products or services provided by the Contract Facility.
- 9.12.2 The quality agreement should define roles of each party in making and maintaining original documents or true copies in accordance with GMP. It should explain how those records will be made readily available for inspection.
- 9.12.3 The agreement should also indicate storage of electronic records in accordance with GMP and immediate retrieval during the required record-keeping time frames established in applicable regulations.

9.13 Change Control Associated with Manufacturing Activities

- 9.13.1 Procedures to be applied in discussion and approval of changes to processes, equipment, test methods, specifications, including allocation of responsibilities for conducting validation activities and other contractual requirements should be defined in this section of the quality agreement.
- 9.13.2 Changes to be reviewed and approved by the Contract Giver before they are implemented and changes that may be implemented by the Contract Acceptor without notifying the Contract Giver should be clearly defined. How all changes are managed should be outlined in the agreement.
- 9.13.3 Both parties should be aware of those changes that need to be submitted to NAFDAC and these should be addressed in the agreement.
- 9.13.4 The quality agreement should address expectations for reporting and approving changes to the following:
 - a. Materials and/or their suppliers
 - b. Establishment locations
 - c. Manufacturing processes
 - d. Products or product types that use the same production line, equipment train, or facility
 - e. Testing procedures
 - f. Major manufacturing equipment
 - g. Shipping methods

Effective Date: 3rd February, 2021

Review Date: 2nd February, 2026

- h. Batch numbering scheme
- i. Container closure systems
- j. Tamper evidence features
- k. Product distribution

9.13.5 The quality agreement should include the expectations of each party for reporting and communication in case of unexpected events and related changes such as manufacturing deviations, complaints, product recalls, adverse event reports, master label changes, field alert reports, process improvement projects, process capability analyses and trending reports.

10. CORRESPONDENCE

All correspondence should be addressed to:

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