ETHIOPIAN FOOD AND DRUG AUTHORITY

GUIDELINES FOR QUALITY AGREEMENT IN PHARMACEUTICAL CONTRACT MANUFACTURING

Document No.	EFDA/GDL/073
Version No.	001
Date of approval	05/05/2025
Date of issue	12/05/2025

Document History

Version No.	Reason for Amendment	Effective Date
001	New Guideline	12/05/2025

Getachew Genete

MMIE LEO

Signature

May, 2025

Addis Ababa, Ethiopia

Foreword

The Ethiopian Food and Drug Authority was established in accordance with Article 66 Sub-Article 2 of the Definition of Powers and Duties of the Executive Organs of the Federal Democratic Republic of Ethiopia Proclamation No. 1263/2021 and its powers and duties are defined by the Council of Ministers Regulation No. 531/2023 with the mission of protecting and promoting public health by ensuring the quality, safety and effectiveness of medical products.

The global practice shows that pharmaceutical manufacturers may not have the capability to perform all manufacturing operations at their own establishments. Hence, they might opt for subcontracting their operations. In such an increasingly complex and diverse industry, the regulation of such practice could not be appropriately managed by the existing regulatory tools as outsourcing of pharmaceutical operation introduces considerable complexity into ensuring compliance with good manufacturing practices. Thus, any activity covered by the GMP guideline that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality.

To provide proper guidance for manufacturers to comply with the legal requirements in involve in contract manufacturing operations, the Authority has found the importance of developing the contract manufacturing of finished pharmaceutical products guideline so as to translate and simplify the implementation of the cGMP requirements stated in the good manufacturing guideline related to contracted out pharmaceutical activities. This Guideline is intended to be used by entities involved in any aspect of pharmaceutical contract manufacturing, packaging and labeling operations. The guideline covers different sections including general principle, role and responsibility of each party involved in contract manufacturing of pharmaceutical products. Pharmaceutical contract givers and contract acceptors are urged to familiarize themselves with these guidelines to ensure that pharmaceutical products are manufactured, packed and labeled in accordance with the regulatory requirements.

Getachew Genete

Medicine Manufacturers Inspection and Enforcement Lead Executive Officer

Acknowledgments

We would like to express our deepest gratitude to the technical working group members who played a pivotal role in developing the Guideline for Contract Manufacturing of Pharmaceutical Products. Their expertise, dedication, and collaborative spirit were instrumental in realizing this comprehensive guideline.

We also extend our sincere appreciation to stakeholders whose insightful comments and constructive feedback significantly enriched the guideline. Your input was invaluable in ensuring that the document meets the highest standards of clarity, relevance, and practicality.

Additionally, we are grateful to workshop participants for their practical perspectives and valuable feedback that greatly contributed to the finalization of this guideline, ensuring it addresses real best practices in contract manufacturing.

Acronyms

CAPA	Corrective Action and Preventive Action
cGMP	current Good Manufacturing Practice
EFDA	Ethiopia Food and Drug Authority
EMA	European Medicine Agency
OOS	Out of Specification
OOT	Out of Trend
PIC/S	Pharmaceutical Inspection Convention/co-operation scheme
WHO	World Health Organization

Definitions

For the purposes of this guideline, the following terms have the meanings hereby assigned to them. They may have different meanings in other contexts.

Bulk Product means any medicine that has undergone all processing stages up to, and produced in large quantities, but excluding, primary, secondary, and tertiary packaging.

Contract Giver means a legal entity who has legal ownership of the finished product or manufacturing facility or market authorization holder of products who will be applying to the EFDA for manufacturing of its product to be carried out by another manufacturer (contract acceptor) on its behalf.

Contract Manufacturer/Contract Acceptor means a legal entity that has a manufacturing facility that engages in pharmaceutical product manufacturing on behalf of other parties (contract giver).

Contract manufacture means the production of a medicine by a manufacturer (the contract acceptor) under the order of and to the specifications of another manufacturer (the contract giver).

Good Manufacturing Practice (GMP) means is that part of quality management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended uses and as required by the marketing Authorization, clinical trial Authorization or product specification.

Finished product means a product that has completed all stages of production, including packaging in its final container and labelling and ready medicine for marketing or use.

Manufacture means all operations involved in transforming raw materials into regulated products under this proclamation including in the preparation, processing, compounding, formulating, filling, packing, packaging, and repackaging.

Manufacturer means a company that carries out operations described under article 2 sub article (54) of the Food and Medicines administration proclamation number 1112/2019.

Marketing Authorization means an official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy and quality of the product.

Parties means contract giver and contract acceptor

Quality agreement means a key regulatory document that focuses on cGMP requirements and other regulatory aspects, sets forth technical details and quality standards, and specifies how parties will work together to control quality, safety and efficacy of contracted products.

Authority means the Ethiopian Food and Drug Authority

1. Introduction

Traditionally, pharmaceutical companies operated under a vertically integrated model, performing all aspects of production internally. However, the growing demand for high performance, coupled with rising operational costs and increasingly complex supply chains, has driven the industry to explore more agile and efficient approaches. One of such approaches is the strategic use of Contract Manufacturing Organizations, which has emerged as a preferred method for streamlining operations and optimizing production processes.

Contract manufacturing involves a formal quality agreement between two parties that clearly defines their respective roles and responsibilities in the manufacturing process. A manufacturer may perform all required operations internally or outsource certain activities to external partners under contractual arrangements. While this approach introduces operational flexibility, it also adds layers of complexity—particularly in ensuring compliance with current Good Manufacturing Practices (cGMP). The Ethiopian Food and Drug Authority (EFDA) requires that all pharmaceutical companies engaged in contract manufacturing meet minimum cGMP standards to ensure the consistent production of high-quality medicines.

The EFDA recognizes the strategic importance of contract manufacturing, especially for those facing challenges such as limited facilities, space constraints, financial limitations, and issues related to cGMP compliance. This is particularly relevant for manufacturers who need to adopt advanced technologies but lack the in-house capacity.

To this end, this guideline establishes the minimum requirements for parties involved in contract manufacturing, packaging, and labeling of pharmaceutical products. It outlines requirements for defining, documenting, and implementing manufacturing responsibilities through quality agreements. These agreements serve as critical tools for ensuring cGMP compliance and maintaining accountability between the contract giver and contract acceptor.

The guidance is intended to assist pharmaceutical manufacturers who seek to contract out part or all of their production processes to compliant contract acceptors, allowing them to maintain product quality while benefiting from operational efficiencies, this approach supports regulatory compliance and strengthens the overall integrity of the pharmaceutical supply chain.

2. Objective

To provide guidance in defining and establishing the relationship between contract giver and contract accepter with applicable laws and regulation and others requirements agreed by both parties for the supply of product

3. Scope

This guideline applies to:

1. Registered medicines in the form of tablet and capsule
2. Both local and abroad manufacturing facilities involved in the manufacturing of bulk manufacturing and finished product manufacturing.

The guideline is not applicable to following manufacturing operations:

1. Partial contract packaging operations (only primary or only secondary/tertiary packaging) of medicinal products.
2. Semi-processed products whose bulk manufacturing process is not completed and are not yet ready for primary, secondary, or tertiary packaging, and
3. Complex products and radio pharmaceuticals.
4. Third party manufacturing

4. General Guidance

4.1. Both Contract giver and acceptor shall be a manufacturer

4.2. Contract giver shall be the Market Authorization Holder

4.3. Products that falls under the agreement shall be registered by EFDA and the market authorization holder shall be the contract giver

4.4. Contract manufacturing must be correctly defined, agreed and controlled in order to avoid misunderstandings

4.5. There must be a written quality contract agreement between the contract giver and the contract acceptor outlining the duties and responsibilities of both parties. The contract agreement shall be a two-party agreement only.

4.6. The contract giver shall have a contract agreement with only one contract acceptor for each product.

4.7. Both parties should be responsible any product quality issue whether it is stated in their agreement or not

4.8. The contract giver and contract acceptor must be manufacturers having a legal entity (manufacturing license) or manufacturers having market authorization in Ethiopia

4.9. The contract acceptor shall be cGMP compliance facility and must be able to satisfactorily carry out the work ordered by the contract giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.

4.10. A contract giver shall provide cGMP compliance certificate or having waiver for cGMP issued by EFDA for bulk pharmaceutical product to be finished in Ethiopia.

4.11. Other agreements signed between the parties shall not contradict the guiding principles and requirements stated in this guideline and other laws governing the pharmaceutical sector.

4.12. All arrangements for contract manufacture, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization of the products.

4.13. The quality agreement shall be accessible and approved by the Authority prior to contract manufacturing services.

5. Responsibility of Parties Involved in Contract Manufacturing

The agreement clearly outlines both individual and shared responsibilities of the involved parties. These responsibilities should be explicitly stated within the quality agreement and serve as a guide for the development of a standardized agreement template between the contracting parties.

5.1. Responsibilities of Contract Giver

The contract giver should be responsible to:

5.1.1. Ensure the quality of the bulk products provided to the contract receiver.

5.1.2. Assess the legality, suitability and competence of the contract acceptor to successfully carry out the outsourced activities.

5.1.3. Ensure that all products and materials delivered by the contract acceptor have been processed in accordance with cGMP and marketing authorization; and that the product has been released by the authorized person.

5.1.4. Provide documentation including cGMP certificate, an approved list of raw material suppliers, validation protocols and reports, batch manufacturing records up to the

packaging operation, shipping records, quality control records, hold time study data, and clinical and non-clinical study reports.

5.1.5. Ensure the stability of the product during transportation, supported by documented evidence.

5.1.6. Provide the contract acceptor with all necessary information (e.g., technical data, standard and requirements of the product or the analytical methods of the product) necessary to carry out the contracted operations correctly in accordance with regulation in force, and the marketing authorization for the product concerned.

5.1.7. Ensure that the contract acceptor is fully aware of any problems associated with the product, the work or tests which might pose a hazard/risk to premises, equipment, personnel, other materials or other products.

5.1.8. Release the product to market or use or dispatch to the customers unless otherwise stated in the agreement.

5.1.9. Periodic quality and compliance systems audits at manufacturing site and should monitor and review the performance of contract acceptor including the implementation of any needed improvements and their effectiveness.

5.1.10. Investigation of product quality issues related to activities at the contract giver and the contract acceptor.

5.1.11. The final decision, after consultation with the contract manufacturer, of whether to conduct a recall.

5.1.12. Ensure that the contract acceptor understands that his or her facilities and activities will be subject to inspection by EFDA or competent regulatory authorities.

5.1.13. Any communication and correspondence with regulatory authorities.

5.2. Responsibilities of Contract Manufacturer/Acceptor

The acceptor should be responsible to:

5.2.1. Ensure the quality of the products from the point of receipt through to manufacturing, packaging and distribution.

5.2.2. Each product manufactured in accordance with agreed processing, testing, and packing procedures and standards and in the same way if amended in accordance with change control procedure.

5.2.3. All products or materials and standards delivered to it are suitable for their intended purposes.

5.2.4. Ensure that the manufacturing process, analytical instrumentation and analytical methodologies are appropriately qualified and/or validated before any routine production begins.

5.2.5. Provide contract giver regulatory submission document relating to the processing and packaging of product.

5.2.6. In the event of any deviation having impact on process and product quality, the contract manufacturer/acceptor should inform the contract giver prior to batch release.

5.2.7. Ensure that all data relevant to the cGMP activities conducted pursuant to this agreement is accurate, controlled and safe from intentional or unintentional manipulation or loss

5.2.8. Any breach of data integrity is investigated and reported in writing to the contract giver. If it affects the quality of the product, it should be reported immediately.

5.2.9. Inform contract giver of any quality system or regulatory authority inspection that may impact on products immediately on receiving notice.

5.2.10. Provide contract giver with copies of all communication and documentation issued by regulatory authority as also such other information pertinent there to, as may be required by contract giver, as agreed time.

5.2.11. The investigation of product quality issues

5.2.12. Based upon the severity of the investigation outcome of the product quality issue, contract acceptor should provide a copy of the completed investigation report to the contract giver such as product compliant and emergency product compliant within agreed time frame.

5.2.13. Refrain from any activity (including unauthorized changes outside the terms of the contract) that may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

5.2.14. Notify contract giver of the first batches and the packaging dates thereof for which the change shall be implemented.

5.2.15. Batch release at the site in accordance with market authorization requirement and manufacturing requirement submitted by a contract giver.

5.2.16. Retain reference samples from each batch of each product and materials.

5.2.17. Provide copies of retained documentation to contract giver within agreed timelines.

5.2.18. A non-disclosure agreement for safety of intellectual property rights.

5.2.19. A qualified person shall be assigned to be responsible for the release of packaged and labeled batches for sale, in accordance with the terms of the contract agreement.

5.2.20. Ensure the quality and stability of the manufactured, packaged medicinal products.

5.2.21. Ensure that an adequate control system is in place.

5.2.22. Ensure that all relevant retention samples are made accessible to the Authority at all reasonable times.

5.2.23. Validate the manufacturing operations.

5.2.24. Ensure suitable environmental conditions during the manufacturing operation.

5.2.25. Comply with the storage requirements as directed by the bulk product manufacturer.

5.3. Shared responsibility of Contract Acceptor and Giver:

Both parties should be responsible to:

5.3.1. Handle product complaints, quality defect investigation and product recall.

5.3.2. Adverse event reporting

5.3.3. Post marketing surveillance.

5.3.4. Handling of issues related to product quality, safety, and efficacy.

6. Content of Quality Agreement

A contract should be drawn up between the contract giver and the contract acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and cGMP and shall be agreed by both parties in written form for submission for application as a guide template. The quality agreement shall include the following contents but not limited to:

6.1. **Definitions** — to ensure that the contract giver and contract acceptor agree on precise meaning of terms in the quality agreement

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

6.3. **Terms and Quality Agreement Review**

6.3.1. This section specifies effective date, review, update and termination of the

quality agreement

6.3.2. Specify who should take the responsibility for the remaining requirements according to applicable law and regulations upon the termination of the quality agreement

6.3.3. This quality agreement shall be version-controlled, i.e., any update shall be marked as a revised version and the date of such version shall be stated and any such version shall be recorded

6.4. **Regulatory Submissions -** this should define who is responsible for

6.4.1. Regulatory submissions for products as applicable.

6.4.2. Specify their roles and cooperation in regulatory submission.

6.4.3. Agreed timeline for regulatory submission

6.4.4. Responsibility for final content, formatting, and wording of such regulatory submissions.

6.4.5. All correspondence, communications/dealings with regulatory authority

6.5. **Materials Management**

6.5.1. This section of a quality agreement shall indicate which party will establish specifications for materials as well as which party will establish processes for auditing, qualifying, and monitoring material suppliers (vendor qualification).

6.5.2. The agreement shall also identify which party will conduct required sampling and testing in compliance with cGMP.

6.5.3. This section of the quality agreement shall address how the parties will ensure appropriate inventory management, including labeling, label printing, inventory reconciliation, and product status identification (e.g., quarantine).

6.5.4. The agreement shall 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.

6.6. **Manufacturing**

6.6.1. Specify the physical address of each outsourced activities will take place

6.6.2. Criteria for the manufacturing of each product

6.6.3. Includes management of OOS, OOT, deviations, CAPA in manufacturing process and reprocessing criteria

6.6.4. Documented and defined process for the destruction of excess, obsolete, or rejected materials.

6.7. **Quality Assurance and Quality Control -** this section of the agreement should define roles and responsibilities of each party for laboratory controls especially in the following areas:

6.7.1. The agreement shall specify responsibility for the quality control and quality assurance of each product, including testing, documentation review, and retention according to the defined and approved procedures/regulations. .

6.7.2. Procedures delineating controls over sampling and testing of samples

6.7.3. 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.

6.7.4. Routine auditing procedures to ensure that a contract facility's laboratory equipment is qualified, calibrated, and maintained in a controlled state in accordance with cGMP.

6.7.5. Designation of responsibility for investigating deviations, non-conformance, discrepancies, out of trends, failures, out of specification results etc.

6.7.6. Define condition in the event of major deviation before batch release

6.7.7. Define responsibility for batch release

6.8. **Documentation**

6.8.1. The quality agreement shall 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.

6.8.2. The quality agreement shall define roles of each party in making and maintaining original documents or true copies in accordance with cGMP. It

should explain how those records will be made readily available for inspection.

6.8.3. The agreement shall also indicate storage of electronic records in accordance with cGMP (data integrity principles) and immediate retrieval during the required record-keeping time frames established in applicable regulations.

6.8.4. Retention of all documentation for the product

6.8.5. Data Integrity

6.8.6. Includes all data relevant for good manufacturing activities conducted pursuant to this agreement is accurate, controlled and safe from intentional or unintentional manipulation or loss

6.8.7. Parties shall agree on procedure, automation system and/or management control must ensure complete data integrity and be assessed regularly

6.8.8. Documentation practices and data handling processes (i.e., paper and electronic) are well defined and they are understood and implemented by all personnel.

6.8.9. Investigation of any breach of data integrity

6.9. **Change Control**

6.9.1. Define initiation, implementation and evaluation of changes

6.9.2. The contract giver and contract manufacturer shall maintain change control systems that assure that all major changes are appropriately agreed with the other party

6.9.3. The major changes that require approval such as but are not limited to site or facility of manufacturer/ testing, batch size, specification test procedure, pharmacopeia changes affecting regulatory filling, expiry/product shelf life, packaging materials and labeling changes,

6.10. **Stability Studies**

6.10.1. Define who is responsible for carrying out and reporting stability testing in accordance with the defined procedures in line with regulatory requirements.

6.10.2. Define responsibilities to evaluate/investigate all OOS stability results or adverse trends.

6.10.3. In the event the quality agreement is terminated, should define who will continue to generate stability data to support the acceptability of product(s) until all products distributed by the contract giver have reached to the end of

their shelf life

6.11. **Periodic Product Review**

6.11.1. Parties shall define who will conduct a periodic quality review of the product in accordance with the defined procedures and regulatory requirements.

6.11.2. Format or template of review report that has to be submitted must be clearly stated

6.12. **Technology Transfer**

6.12.1. Define responsibility of each activity for technology transfer such as but not limited to, validation and qualification activities, cGMP controls and specifications, equipment selection and procurement, method validation transfer, and risk control and mitigation study

6.12.2. cGMP procedures and documentation, batch record transfers, cleaning validation studies and limits, on cGMP-based engineering runs and optimization studies

6.13. **Inspection and Audit**

6.13.1. Specify their roles related to regulatory inspection and audit

6.13.2. Agree on the response and any improvement plan to any adverse observations relating to the products or their manufacture, prior to these being submitted to the regulatory authority.

6.13.3. Audits by the contract giver and contract acceptor

a) Define agreed plan of regular inspection and audit, report and response time line on audit observation

b) Agree on time line on quality and compliance improvement plan and regularly review the implementation of the plan

6.14. **Product Recall**

6.14.1. Agree on recall of any products in contract manufacturing in the market

6.14.2. Initiation, investigation and final decision of recall and to meet required regulatory timeline

6.14.3. Define responsibility for any communication with regulatory authorities

6.14.4. The coordination and management of any recall situation

6.14.5. State that recalled product secure storage and destruction

6.15. **Qualification and Validation**

6.15.1. Include process, equipment, system and analytical method validation and qualification

6.15.2. The agreement shall 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 cGMP.

6.15.3. The agreement also shall identify which party will approve equipment validation, qualification, and maintenance activities.

6.15.4. The agreement shall indicate how the parties will communicate information about preventing cross-contamination and maintaining traceability includes risk assessment reports when a contract acceptor processes drugs for multiple organizations.

6.15.5. The agreement shall indicate cleaning validation. The validation shall be updated to cover any new products made in the same facilities as those facilities used to manufacture product for the exclusive distribution to contract giver

6.16. **Storage and Shipping**

6.16.1. The agreement shall include who will do these activities, the party involved will ensure that during packaging, storage, and shipment of the products that there is no possibility of deterioration, contamination, or mixing with any other materials.

6.17. **Governing Law and Dispute Resolution**

6.17.1. The interpretation and construction of this quality agreement shall be governed by applicable law and regulation

6.17.2. Any conflict resolution related to the outsourced activities and products related issue should state in the agreement

References

1. The Food and Medicine Administration Proclamation No. 1112/2019, Addis Ababa, Ethiopia
2. EFDA, GMP inspection guidelines 3nd edition, 2024
3. FDA, U.S. Department of Health and Human Services Food and Drug Administration Contract Manufacturing Arrangements for Drugs: Quality Agreements Guidance for Industry, November 2016
4. EMA, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human guideline Q7 good manufacturing practice guide for active pharmaceutical ingredients
5. EMA, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human guideline Q9 Quality Risk Management Q9 (R1).18 November 2021
6. EMA, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human guideline Q10 on pharmaceutical quality system, 28/05/2014
7. EMA, PIC/S GMP guide in part 1, chapter 7, 2023
8. WHO, Good Pharmaceutical Manufacturing Practices annex 2, chapter 7, October, 2014