A Review on Quality Agreement requirement in Pharmaceuticals by Regulatory Authority in Compliance to cGMP Guidelines

Suleman S khoja [1],Sohil S khoja [1], Farhad S Khoja [2],Shamim S Khoja[2], Narmin A Pirani[2]
[1] Resource person in Pharmaceutical Quality Assurance and Facility Audit,
Vapi,, Gujarat, India.
[2] Registered Pharmacist,
Gujarat State Pharmacy Council, Gujarat.
* premukhoja@gmail.com

ABSTRACT

A quality agreement is a comprehensive written agreement between parties involved in the contract manufacturing of drugs that defines and establishes each party's manufacturing activities in terms of how each will comply with CGMP. Quality agreements may be reviewed during inspections. A quality agreement describes the owner's and the contract facility's roles and manufacturing activities under CGMP. The quality agreement should explain how the contractor will report manufacturing deviations to the owner, as well as how deviations will be investigated, documented, and resolved in compliance with CGMP. Quality agreements should state that manufacturing services provided by contract facilities (including laboratories) will comply with CGMP. The most critical pieces are quality and change control, as described in the following sections. Manufacturing Activities Change Control Associated With Manufacturing Activities.

Keywords: Regulatory Authority, Compliance, cGMP Guidelines, Quality Agreement

INTRODUCTION

Quality Agreement: A quality agreement is a comprehensive written agreement between parties involved in the contract manufacturing of drugs that defines and establishes each party's manufacturing activities in terms of how each will comply with CGMP.

Objective

- *Commercial manufacturing* refers to manufacturing processes that result in a drug or drugs intended to be marketed, distributed, or sold.
- *Commercial manufacturing* does not include research and development activities, manufacturing of material for investigational new drug studies (e.g., clinical trials, expanded access), or manufacturing of material for veterinary investigational drugs. Although this guidance does not explicitly apply to the manufacture of investigational, developmental, or clinical trial materials, FDA believes that quality agreements can be extremely valuable in delineating the activities of all parties involved in contract research and development arrangements. Many of the principles described in this guidance could be applied in pre-commercial stages of the pharmaceutical life cycle.

QUALITY AGREEMENTS MAY BE REVIEWED DURING INSPECTIONS

Terms and Definition:

Owners: as manufacturers of APIs, drug substances, in-process materials, finished drug products, including biological products, and combination products

Contract facilities: as parties that perform one or more manufacturing operations on behalf of an owner or owners.

Documentation as per CGMP [1-4]

- Agreement.
- Roles and Responsibility.
- Activity.
- Timeline for Completion of Query /Complain.
- Design and Sharing of Complete Investigation and process and in accordance to compliance.
- Audit compliance.

How to cite this article: Khoja SS,Khoja S, Khoja FS,Khoja S, Pirani NA; A Review on Quality Agreement requirement in Pharmaceuticals by Regulatory Authority in Compliance to cGMP Guidelines; PharmaTutor; 2017; 5(5); 24-28

ELEMENTS OF A QUALITY AGREEMENT [4-7]

A quality agreement describes the owner's and the contract facility's roles and manufacturing activities under CGMP. A well-written quality agreement will use clear language. It will define key manufacturing roles and responsibilities. It will establish expectations for communication, providing key contacts for both parties. It will specify which products and/or services the owner expects from the contract facility and who has final approval for various activities. Most quality agreements contain the following sections:

- Purpose/Scope— to cover the nature of the contract manufacturing services to be provided
- Definitions — to ensure that the owner and contract facility agree on precise meaning of terms in the quality agreement
- Resolution of disagreements — to explain how the parties will resolve disagreements about product quality issues or other problems
- Manufacturing activities — to document quality unit and other activities associated with manufacturing processes as well as control of changes to manufacturing processes
- Life cycle of, and revisions to, the quality agreement.

The quality agreement should explain how the contractor will report manufacturing deviations to the owner, as well as how deviations will be investigated, documented, and resolved in compliance with CGMP. Quality agreements should state that manufacturing services provided by contract facilities (including laboratories) will comply with CGMP.

The most critical pieces are quality and change control, as described in the following sections.

- *Manufacturing Activities*
- *Change Control Associated With Manufacturing Activities*

Classification of Quality Agreement

1) Manufacturing Activities	2) Change Control Associated With Manufacturing Activities
Quality unit activities Facilities and equipment Materials management Product-specific considerations Laboratory controls Documentation	Either an owner Contract facility

1) MANUFACTURING ACTIVITIES

Quality agreements may document each party's roles and manufacturing activities with a variety of formats — charts, matrices, narratives, or a combination of these. Regardless of the format, a quality agreement should clearly document which party is responsible for specific activities.

No party (Vendor /Service Provider) to a quality agreement may delegate any of its responsibilities to comply with CGMP through the quality agreement or any other means.

The quality agreement should cover all of the activities for ensuring compliance with CGMP. Depending on the scope of the contract manufacturing services to be provided, the quality agreement should indicate whether the owner or contract facility (or both) will handle specific activities related to each.

Quality unit activities: This section of a quality agreement that addresses each party's quality unit activities should define in detail how the parties will work together to ensure that products are manufactured in compliance with CGMP. Note that assigning quality control or other activities to either the owner or contract facility in the quality agreement does not relieve either party from compliance with applicable CGMP requirements.

In particular, this section of the quality agreement 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).22 In addition, owners are responsible for approving or rejecting drugs manufactured by the contract facility,23 including for final release. In all cases, the owner must not introduce or deliver into interstate commerce, or cause to be introduced or delivered into interstate commerce, any drugs that are

adulterated or misbranded. Within its quality unit activities, a quality agreement should describe how and when the owner and contract facility will communicate with each other, both verbally and in writing. This includes identifying appropriate contact personnel within the owner's and contract facility's organization

Quality agreements should also cover audits, inspections, and communication of findings. The agreement should allow owners to evaluate and audit contract facilities to ensure CGMP compliance for specific operations. This provision should cover both routine quality audits and for-cause audits. The agreement should also set owner and contract facility expectations regarding FDA inspections (pre-approval, routine surveillance, and for-cause) with consideration for the nature of the products to be manufactured and/or services to be provided. It should include the parties' agreed-upon provisions for communicating inspection observations and findings, as well as relevant FDA actions and correspondence.

Because contract facilities often provide services to multiple owners, the quality agreement should address when, how, and what information the contractor will report to owners about objectionable conditions observed during inspections and audits of the contract facility.

Facilities and equipment:

A quality agreement should identify the specific site(s) where the contract facility will perform manufacturing operations, including the address of and specific services to be provided at each site. It 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 CGMP. The agreement also should identify which party will approve equipment validation, qualification, and maintenance activities. In addition, it should indicate how the parties will communicate information about preventing cross-contamination and maintaining traceability when a contract facility processes drugs for multiple owners.

Materials management:

Quality agreement should indicate which party will establish specifications for components as well as which party will establish processes for auditing, qualifying, and monitoring component suppliers. It should also identify which party will conduct required sampling and testing in compliance with CGMP. 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). The agreement should address how the contract facility will prevent mix-ups and cross-contamination. FDA does not expect the agreement to contain a complete description of the supply chain for each component. However, the agreement should define responsibility for physical control of materials at different points in the manufacturing process. For example, the quality agreement should cover responsibilities for proper conditions for storing and transporting or shipping materials. It should define each party's roles in storage and transport — whether from the contract facility back to the owner or to another contract facility for further operations. This includes defining activities for monitoring or validating shipping conditions as appropriate.

Product-specific considerations:

A comprehensive quality agreement may address specific considerations related to individual products. The owner and contract facility might opt to include this information in an appendix, or directly in the body of the quality agreement. In either case, if included, this section of the quality agreement should include the parties' expectations of each other regarding:

- Product/component specifications
- Defined manufacturing operations, including batch numbering processes
- Responsibilities for expiration/retest dating, storage and shipment, and lot disposition
- Responsibilities for process validation, including design, qualification, and ongoing verification and monitoring

• Provisions to allow owner personnel access to the contract facility when appropriate

The quality agreement also should indicate how owners will transfer knowledge, such as product and process development information, to contract facilities to ensure a drug can be manufactured in compliance with CGMP, and conversely how contract facilities should share with owner's product quality information gained throughout the product life cycle. This applies to knowledge about all drugs, including drugs subject to an approved application (e.g., new drug application) and nonprescription drug products marketed under an over-the-counter drug monograph.

Owners that hold an approved drug application should be aware of application and approval requirements that could affect manufacturing activities. Both parties to a quality agreement should share relevant information to ensure compliance with CGMP and other applicable requirements of the FD&C Act.

Laboratory controls:

Testing of their drugs. A quality agreement will help each party meet this need by defining roles and responsibilities for laboratory controls. We recommend the following elements:

• Procedures delineating controls over sampling and testing samples

• Protocols and procedures for communicating all laboratory test results conducted by contract facilities to the owner for evaluation and consideration in final product disposition decisions

• Procedures to verify that both owner and contract facilities accurately transfer development, qualification, and validation methods when an owner uses a contract facility for laboratory testing

• 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

Designation of responsibility for investigating deviations, discrepancies, failures, out-of-specification results,25 and out-of-trend results in the laboratory, and for sharing reports of such investigations .

Documentation: The quality agreement should define expectations between the contract facility and the owner to review and approve documents. It also should 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. The quality agreement should also define owners' and contract facilities' roles 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.

The quality agreement also should indicate that electronic records will be stored in accordance with CGMP and will be immediately retrievable during the required record-keeping time frames established in applicable regulations.

2) CHANGE CONTROL ASSOCIATED WITH MANUFACTURING ACTIVITIES:

An owner or a contract facility may initiate changes to processes, equipment, test methods, specifications, and other contractual requirements. Both parties should discuss changes and address them in the quality agreement. There are some changes that owners should review and approve before they are implemented and other changes contractors may implement without notifying the owner. How all changes are managed should be outlined in the agreement, including allocation of responsibilities for conducting validation activities as needed before implementing changes. Additionally, both parties should be aware of those changes that need to be submitted to FDA in a supplement or annual report. The owner and contract facility should carefully consider and agree on the types of changes to report to each other and to FDA and the need for approval from each party's quality unit and FDA, as applicable. [7-8]

The quality agreement should address expectations for reporting and approving changes to the following:

• Components and/or their suppliers

• Establishment locations

• Manufacturing processes

• Products or product types that use the same production line, equipment train, or facility

• Testing procedures

• Major manufacturing equipment
• Shipping methods
• Lot numbering scheme
• Container closure systems
• Tamper evidence features
• Product distribution

Various unexpected events, such as manufacturing deviations, complaints, product recalls, adverse event reports, master label changes, field alert reports, and biological product deviation reports, may necessitate changes to processes and procedures. Process improvement projects, process capability analyses, and trending reports may also necessitate changes to processes and procedures. The quality agreement should include the owner's and contract facility's expectations for reporting and communication in case of unexpected events and related changes

What to exclude from a Quality Agreement is also worth mentioning. Certain items that should never appear in a Quality Agreement include:

- general business terms and conditions,
- pricing and escalator clauses,
- forecasting,
- delivery terms,
- confidentiality obligations,
- liability limitations

FORMAT /PROTOCOL EVERY INDUSTRY MUST INCLUDE IN STANDARD OPERATING PROCEDURE FOR QUALITY AGREEMENT WITH CONTRACTOR:

- Site specific Format for Supplier/contractor Qualification and Approval by Site Quality Head and User Team.
- Audit Reporting Format for Site person before Approval with External Facility Audit Team (If any)
- Minutes of Meeting (MoM) Format.

CONCLUSION

Recommendation as per Regulatory Compliance Owners and contract facilities can draw on quality management principles to carry out the complicated process of contract drug manufacturing by defining, establishing, and documenting their activities in drug manufacturing operations, including processing, packing, holding, labeling operations, testing, and quality control operations. Accordingly, FDA recommends that owners and contract facilities implement written quality agreements as tools to delineate manufacturing activities for ensuring compliance with CGMP.

REFERENCES

1. Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients
2. Q9 Quality Risk Management
3. Q10 Pharmaceutical Quality System
4. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
5.http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
6. http://www.gmp7.com/gmp-technical-agreement_cm494.html
7. http://apic.cefic.org/pub/qualityagreementguideline_final_200912_clean.pdf
8. http://www.mastercontrol.com/newsletter/quality_agreements_1209.html