

## **A Model for Pharmaceutical Supply Chain Quality Agreements**

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### **The Evolution of the Quality Agreement**

Over a decade ago, the way business was conducted between pharmaceutical manufacturing companies and their supply chain providers was typically expressed through verbal expectations at the due diligence meeting, at the audit, or at the first project meeting, and they were pretty much done by written bullet points.

Today, successful sponsor companies regard the vendor company as a partner. Experienced sponsors expect their partners to be a part of their team. The expectation is that they will guide them in areas where their team members are new, inexperienced, or still learning.

Sponsors and vendors learned that one of the better ways to succeed was to clearly establish project expectations and put them into a **Master Service Agreement** between both parties. As the MSA became more popular, legal departments became part of MSA process. In order to avoid liability, the vendor became less of a partner and more of a business associate looking to avoid legal action and liability.

Addendums to the MSAs were written to avoid having separate MSAs for each project. These eventually morphed into what would be called the **Technical Agreement**. The parts of the Technical Agreement included, but were not limited to, purpose and scope, definitions, responsibilities, contact list/points of contact, list of products/components, approval process, changes and revisions, and a list of subcontract laboratories/manufacturing companies.

The challenge of any agreement between sponsors and their vendors was the number of people involved in the process execution. Understanding roles and responsibilities, expectations and deliverables, created many issues and delays.

The **Quality Agreement** evolved to fill these gaps and address these challenges.

### **Regulatory Guidance and Best Practices**

Regulatory agencies around the globe have defined A Quality Agreement (QA) as a written document outlining the roles and responsibilities for the owner of the drug and the Contract Manufacturing Organization (CMO) in terms of basic cGMP regulations. (1-14)

Although regulators reference contracts and agreements interchangeably in their guidance documents, it is important to understand that the intent of such documents is to formalize the relationship between organizations within the supply chain from a quality perspective.

The concept is implemented for the Good Supply Chain Practices (GSCP) and Good Distribution Practices (GDP). Although currently not required by their regulations, the FDA has issued draft guidance for the industry regarding contract manufacturing arrangements for drug. (2)

However, regulatory citations, including warning letters, have already been issued by the FDA to companies that failed to set up or did not follow such Quality Agreements with their pharmaceutical manufacturing companies, and their supply chain providers. (15)

Hence, for good business practice and to avoid regulatory citation, it is no longer enough to have “purchasing agreements” with supply chain stakeholders. The industry should have, comprehensive Pharmaceutical Supply Chain Quality Agreements. The Quality Agreement, generally speaking, but not limited to, should be used as a tool for communication. This may include, but is not limited to, monitoring and tracking activities, chain of custody monitoring, shipment requirements, turnaround time, shipping processes, customs challenges, regulatory handling, security systems, validation of shipping package design, oversight of supply chain partners, proactive risk assessment and contingency planning, training and qualification of staff, supply chain management processes, and frequency of partner audits.

The results of independent Market research conducted by the Avoca Group in 2013 (Table 1) on quality in the delivery of clinical supply chain services show that there is a gap as far as the use of the Quality Agreement and the awareness that regulators are scrutinizing it(16).

One of the first requests usually asked in an internal quality assurance audit or a regulatory inspection for cGMP is to review the Quality Management System, including the Deviation Report and its related corrective action and preventive action (CAPA) documents. Recently, however, inspectors have been paying additional focus on current good distribution practices (cGDP). In this latter focus, regulators are now requesting to see, review and confirm the implementation of these Quality Agreements. It is important to carefully map the supply chain and identify all stakeholders. These may include in-house suppliers of product and external partners such as logistics (thermal solutions, reverse logistics, recalls), carriers, freight forwarders, airports, customs, warehouses, pharmacies, study coordinators, clinical investigators, depot managers, and others. The Quality Agreement should, therefore, be tailored to address the specific supply chain being used.

The FDA considers the cGDP as an extension of the cGMP (5). However, there are several global laws and regulations that should be considered (6 – 14). This will ensure meeting the local and destination regulatory requirements.

## **Structure and Content of Supply Chain Quality Agreement**

The parties of the Quality Agreement, namely the Sponsor or Owner and Contractor, should discuss, agree upon, and document the roles and responsibilities of each involved party. The authors recommend that the reader select the appropriate sections, eliminating or adding topics, as needed for the specific project, in the Quality Agreement. This will depend on the particular supply chain and activities of each of its members. Whilst such a comprehensive list may seem intimidating at first, the authors expect that a comprehensive document is possible, especially when developed with the support of internal quality stakeholders and in consultation with subject matter experts from our industry.

1. Effective Date
2. Part of Master-Service Agreement (MSA)
3. Purpose
  - a. Quality Systems
4. Scope
  - a. Services Listed
  - b. Regulatory Compliance and Standards
  - c. Project Plan
  - d. Conflicts and Exclusions
5. Contact Information-Appendix 1
6. Quality Systems
  - a. Management Commitment and Responsibilities
  - b. Regulatory Compliance
    1. -Geography
    2. -Local/Global
  - c. Supply Chain Management Services
  - d. Master Validation Plan
  - e. Training
    1. Documents
    2. Testing to show learning
    3. -SOPs
7. Client Audits
  - a. Frequency (Annual or Bi-Annual)
  - b. Charges
  - c. Response to Audit Observations
8. Regulatory Authority Audits (e.g. FDA)
  - a. Product
  - b. General
  - c. For Cause
9. Internal Audits
  - a. QA
10. Supplier Audits (on behalf of clients)
  - a. Sub-Contractor
  - b. Systems
  - c. Materials
  - d. Services
11. Disposition
  - a. Documents
  - b. Label Content (for Temperature)

- c. Formulation (Dynamic Stability, e.g. Vibration, Drop, Pressure, Temperature, Humidity)
  - d. Master Batch Record
  - e. Deviations (Planned or Unplanned)
  - f. Investigations
- 12. Document Control/Change Control System-SOP
- 13. Record Retention System-SOP
- 14. Storage and Movement of Inventory
- 15. Mode of Transportation
  - a. Ground, Air, Sea, Rail
  - b. Requirements (DOT, FAA, ADR)
- 16. Specialist, Integrator, Expeditor, Freight Forwarder, Carrier
  - a. Domestic/International
  - b. Customs Clearance
- 17. Depot System
- 18 Drop Shipment
- 19 Thermal Mapping
- 20 Temperature/Humidity Monitoring
- 21 Qualified Vehicles, Aircraft, Sea Containers
- 22 SOPs to be Used
- 23 Notifications
- 24 Security
  - a. Driver Identification
  - b. -Escort Vehicles
  - c. -Overt and Covert Tools and Devices
  - d. -Geo-Fencing and Tracking
  - e. -Driver's Program
    - i. \*Truck Completely Fueled
    - ii. \*No stop Until Destination or After 200 Miles
      - a. Truck is Sealed
    - iii. \*Shipment is Monitored At All Times by a Team of Two Drivers if Needed
    - iv. \*Restricted Sharing of Shipment Details to Authorized Personnel
- 25 Secure Parking
  - a. -Overnight
  - b. -Transfer to Another Vehicle
  - c. -Waiting Delivery
  - d. -Gated Fenced Yard
  - e. -Twenty-Four Hour Guard and Surveillance Systems
- 26 Confidentiality Agreement (CDA)
  - a. -Communication
  - b. -Records

- c. -SOPs
  - d. –Proprietary knowledge
  - e. -Testing Protocols, Results, and Reports
- 27 Breach or Default of Quality Practices
  - a. –Why, What, When, and How to rectify (Not Who!)
- 28 Liability
  - a. -Total
  - b. -Cargo
  - c. -Terms
  - d. -Tariff
  - e. -Service Guide
- 29 Special Considerations
  - a. -Required Signature
  - b. -Delivery at Certain Time (am/pm)
  - c. -Study Coordinator
  - d. -Time Out of Refrigeration (Per Incident and Cumulative)
  - e. -Details of Pre-Coordinated Activities
- 30 Change Control (Client and Service Provider)
  - a. -Process and SOP
  - b. -QA Approval
- 31 Corrective Action and Prevention Action (CAPA)
- 32 Tracking of Audit Observations and Responses – In the Form of a Management Action Plan (MAP) with Timelines and Responsible Parties)
- 33 Retention Samples
  - a. -Storage Conditions
  - b. -Project Plan
  - c. -Quantity
  - d. -Duration
  - e. -Annual Review dates
- 34 Complaint Handling
  - a. -Clients
  - b. -Service Providers
  - c. -Quality Contact
  - d. -End User
- 35 Recoveries and Recalls
  - a. -Role and Responsibilities
  - b. -Retrieval Documents
- 36 SOPs
  - a. -Document Requirements to Perform Compliant Services
- 37 Products to Which this Quality Agreement Applies
- 38 Process to Which this Quality Agreement Applies

- 39 Service Provider Procedures References
- 40 Definitions/Lexicon
- 41 Revision History
  - a. -Number
  - b. -Effective Date
  - c. -Reason for Revision
- 42 Project Manager or Main Contact Person
- 43 Approval and Execution
  - a. -Function
  - b. -Client
  - c. -Service Provider
  - d. -QA Signature and Printed Name
  - e. -Management Signature and Printed Name
- 44 Appendix 1-Contact Information
  - i. -Name
  - ii. -Title
  - iii. -Department
  - iv. -e-Mail Address
  - v. -Phone
  - b. -Office
    - Cell
    - Pager
    - Fax

## Conclusion

It is important for the reader to understand the position of all major regulatory bodies and the explicit and implicit requirements for having a well written and executed Quality Agreement.

*"Written Quality Agreements are not explicitly required under existing cGMP regulations and do not relieve either party of their responsibilities under cGMP regulations or under the Act. However, Owners and Contracted Facilities can draw on quality management principles to carry out the complicated process of contract drug manufacturing by defining, establishing, and documenting the responsibilities of all parties involved in drug manufacturing, testing, or other support operations.*

*Accordingly, FDA recommends that Owners and Contracted Facilities implement written Quality Agreements as a tool to delineate responsibilities and assure the quality, safety, and effectiveness of drug products." (2)*

## **Acknowledgment**

The authors would like to thank **Robert H. Seevers**, PhD, Eli Lilly and Company, and **Bruce Guenter**, Pfizer for their review and comments in preparing the manuscript of this article.

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#### *Table 1*

*Market research conducted by the Avoca Group on quality in delivery of clinical supply chain services.*

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#### **Respondent by Market sector**

Sponsor Company	56%
Clinical Manufacturing Organization (CMO)	9%
Central Laboratory	13%
Contract Research Organization (CRO)	14%
Clinical Supply Packaging company	5%
Other	3%

#### **Respondent by Region**

North America (other than Mexico)	44%
Europe	35%
Asia Pacific	14%
Latin America	5%
Africa	2%



### **Implementation and Awareness**

Always use Quality Agreement	40%
Used Quality Agreement from time to time	32%
Used their own standard corporate template	41%
Were aware the Quality Agreements are now scrutinized by the FDA	33%

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