WHITE PAPER PRESENTED BY PREMIER RESEARCH

Pharma Quality Agreements: What Are They, and Why They Matter For Your Study

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ABSTRACT

Quality Agreements are an effective bridge to a successful future for companies in the drug development sector – putting one in place at the start of the business relationship can prevent problems later. Quality Agreements mitigate risk and increase collaboration between partners. These agreements define the timelines and establishes responsibility and accountability. They supplement contractual commitments. In addition to making good regulatory sense in ensuring GCP compliance, they also make good business sense and can potentially save the sponsor time and money.

QUALITY ASSURANCE

Introduction

Quality Agreements have been utilized in the pharmaceutical industry for many years to describe responsibilities contracted out to vendors providing GMP services like contract manufacturing, packaging, and distributing. Quality Agreements are just beginning to be utilized in the clinical drug development sector to ensure responsibilities are understood by both the contractor and the vendor providing GCP services. Pharmaceutical and biopharmaceutical industries are relying on Quality Agreements more often and the FDA is recognizing the importance to demonstrate proper oversight and compliance. This white paper focuses on the Quality Agreements in the GCP world.

In today's environment of virtual companies and outsourced drug development, it is important to maintain and demonstrate proper oversight to regulatory authorities. With release of the ICH/GCP E-6 (R2) 2016 addendum, sponsors are also required to demonstrate adequate vendor oversight of CROs, including those sub-contracted to another party by the sponsor CRO(s). A Quality Agreement is the perfect tool to outline responsibilities and expectations. A Quality Agreement in the scope of pharmaceutical development is an agreement that is mutually negotiated and concluded between the Quality Departments of a sponsor (Pharma Company) and their vendors (CROs, etc.). It is intended to define responsibilities relative to quality tasks and help ensure the development of safe products. Contract partnerships inevitably have issues and Quality Agreements ensure they're dealt with quickly and systematically.

Written contracts or agreements defining the responsibilities and communication processes for quality related activities of the involved parties are mandatory for "contract manufactures" or "outsourced activities". In principle, it is the responsibility of the contract giver to request the closure of such a contract or agreement with its contract acceptors.

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What is a Quality Agreement?

A Quality Agreement is a tool to clearly delineate GCP responsibilities between a sponsor and a contractor that assists companies and their contractors in avoiding certain conflicts. Companies can prevent problems later by putting a Quality Agreement in place at the start of the business relationship. The Quality Agreement documents the roles and responsibilities, expectations, timelines, deliverables, and quality standards between the "contract provider" and the "contract acceptor".

Each party has a role and responsibility; the agreement is not a one-sided document. The Quality Agreement communicates expectations to the sponsor and the vendor. The Quality Agreement is the responsibility of the quality assurance (QA) function of both sponsor and vendor companies. Although the agreement is typically the responsibility of QA, when drafting a Quality Agreement, the author should solicit input from other functional areas/stakeholders including legal.

The author of the Quality Agreement is typically a Quality Risk Manager (QRM). This is the person designated as the conduit between the companies to ensure precise and effective communication. The QRM solicits input and review from the following stakeholders:

+ Clinical team (project manager, clinical development director, managers, etc.)
+ Purchasing or procurement
+ Legal

Most contractors prefer this one contact approach because it lessens confusion that can result from diverse opinions or viewpoints. The QRM should focus on the objective of the Quality Agreement. Remember that the Quality Agreement is not a supply/service/technical agreement. It is typically a stand-alone document to delineate the GCP responsibilities and the scope of the specific supply or service. The Quality Agreement should contain the specific details to ensure responsibilities are clearly outlined for both vendor and contractor.

The Quality Agreement provides the transparency of quality, yet documents the oversight of both the sponsor company and vendor company by:

+ Establishing good communication with the vendor through effective relationship management
+ Defining the sponsor and vendor responsibilities from the outset (planned)
+ Understanding who does what, when, where and how it is to be communicated
+ Considerations when assessing a new vendor

The company implementing a Quality Agreement should begin by considering its scope. Once understood, the outline including the basic elements of the Quality Agreement can be utilized to draft the agreement. A well-developed Quality Agreement ensures that both parties in an outsourcing situation uphold product integrity—but only if the agreement is constructed well and is followed. A well written Quality Agreement will lead to successful partnerships.

Types of Pharma Quality Agreements

Type of Contractor/Vendor	Service Provided
Manufacturer	A facility that manufactures active pharmaceutical products (API), excipients, or formulated product
Laboratory	Laboratory that performs tests or assays on: + GLP or clinical samples + Stability samples + Release assays and provides CofAs + Assay development + Expiry dating of investigational products
Stability Storage Facility	A facility that stores APIs, excipients, clinical trial materials, and/or finished product, and maintains storage conditions at set protocols
Raw Material Supplier	A provider of raw materials utilized to manufacture API or API intermediates
Excipients Supplier	A supplier of excipients used in the drug product formulation
Packaging Facility	A facility that packages clinical materials and/or finished drug product
Distribution Facility	A facility that distributes clinical trial products and/or finished product
CRO	A contract research organization (CRO) is an organization that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis

Elements to consider when developing a Quality Agreement:

+ Determine who in QA will draft the Quality Agreement (When possible, a single functional unit should speak for the entire company)
+ Determine who negotiates the content of the Quality Agreement
+ Negotiate cost and ownership of investigations
+ Clear language about how the sponsor will qualify and document their approvals
+ Describe consequences of delayed communication
+ Document who is to be notified of suspect or potential fraud or scientific misconduct investigations
+ Provide timelines for notifications
+ Outline how resolutions will be documented (providing the who, when, how documentation)
+ Outline deviation management
+ Describe change management

List the SOPs that will be utilized in the Quality Agreement:

+ Sponsor SOPs
+ Vendor SOPS
+ Hybrid of both select sponsor and vendor SOPs

Ensure training on appropriate SOPs is documented when required. Ensure training on the Quality Agreement is documented and provide direction on the filing and access to the agreement for stakeholders/functional departments.

The Quality Agreement Document

It is generally recommended that the wording of Quality Agreements be kept simple and non-legal for the most part. However, a legal review of the final draft agreement is a must, since the Quality Agreement is typically a stand-alone document. It may be negotiated at the same time as the Master Service Agreement (MSA) is negotiated however, using it as an addendum to a MSA is not recommended. Not having the Quality Agreement undergo a qualified review by a legal department may expose the company to potential liability. It is, however, not the Legal Representative's task to interpret GCPs and change the language unless potential liability exists. It is their job to look at the document from the point-of-view of someone who is providing a level of protection to the company as a whole.

Benefits of a Quality Agreement in the GCP Setting

+ Ensures GCP compliance and aligns with the new ICH E6 (R2) by providing documented oversight by sponsors
+ Provides an effective collaboration between compliance and clinical development teams
+ Streamlines GCP compliance throughout companies
+ Enhances the sponsor/service provider relationship
+ Integrates effective training elements into the agreement to ensure vendors are true partners with more transparency
+ Provides collaboration to achieve compliance and quality within the clinical process
+ Ensures documented collaboration and oversight

Key Performance Indicators for Compliance through Quality Agreements

A properly executed Quality Agreement will describe and outline responsibilities to eliminate misunderstandings. A quality agreement demonstrates planning and commitment of both sponsors and vendors/CROs.

Contract partnerships inevitably have some issues, and Quality Agreements ensure they're dealt with quickly, efficiently, and systematically. Key performance indicators can be an effective tool as part of the Quality Agreement.

+ Develop and define compliance metrics from quality assurance audit observations
+ Analyze initial data to develop key performance indicators
+ Provide ongoing assessments of continuous quality improvement
+ Develop strategies for conducting and learning from trending non-compliance data
+ Identify the number and types of audits that will be conducted during the project
+ Determine when to change the scope and approach of audits to meet compliance demands

Developing key performance indicators that both the contractor and sponsor agree to from the beginning of the collaboration is essential to managing risks. These indicators measure the performance and allow for continuous improvements to be initiated and tracked. The Auditing Department performs audits and provides data that can be utilized to ensure appropriate quality oversight of both companies. The FDA frowns on repeat findings with repeat corrective actions without appropriate oversight and measures taken to prevent reoccurrence. Tracking audit findings across regions and observation categories can indicate areas of concern when the same findings are detected over and again.

The Quality Agreement provides a means to track and trend data that can be utilized in quality improvement initiatives. The quality agreement can outline how often a project's audit findings will be shared and what type of report will be generated and distributed to ensure corrective and preventive actions are effective. Both companies benefit from assessing the continuous quality improvements. These should be negotiated during the proposal stage to ensure proper resources are available for implementation.

The Quality Agreement is intended to define responsibilities relative to quality tasks to assure the development of safe products. A Quality Agreement is based on the quality procedures in place at both the sponsor and CRO. The Quality Agreement also includes commitments between the parties regarding the provision of information, documents and communication and notification rules including contacts. It creates mutual understanding of the quality and regulatory requirements relevant obligations related to quality. By clearly delineating responsibilities, costly product quality issues resulting from miscommunication can be reduced or eliminated.

The negotiation and review of a Quality Agreement should always be a collaborative effort of different departments of the parties involved. The quality representatives negotiate and review the quality sections, and legal representatives negotiate and review the legal provisions. Other departments (e.g., Purchasing, Business Development) may be involved as appropriate. Keep in mind that it is highly recommended to have a sole person in the negotiation phase, preferably from the Quality Assurance, to act as the voice of the entire company.

Challenges to companies in developing Quality Agreements

+ Limited resources
+ No Quality Assurance Department
+ Selecting, qualifying and managing clinical vendors needs to be outsourced
+ Small to mid-size companies may operate as virtual companies and need to outsource all functions of development including QA
+ Quality Agreements can provide the documented oversight needed to ensure management and oversight is maintained through the project life cycle

Integrating effective training elements into the Quality Agreement will:

+ Ensure the partnership between contractor and vendor is well documented and understood
+ Determine if different interpretations of GCP compliance exist that can be discussed early on to ensure a consistent approach to guidelines

Conclusion

Conflict costs money! Incorporating Quality Agreements into your project while taking a risk based approach to define oversight and expectation from the start will drive consistency and avoid pitfalls. Far too often, easily preventable situations grow into irreconcilable differences between a sponsor and contractor that fail to benefit either party. Putting a sound Quality Agreement in place at the start of the business relationship can prevent problems later.

Quality Agreements mitigate risk and increase collaboration between partners. Established early in the relationship, the Quality Agreement defines the timelines and establishes responsibility and accountability. Quality Agreements supplement contractual commitments.

Formal Quality Agreements with contractors not only make good regulatory sense in ensuring GCP compliance, they also make good business sense and can potentially save the sponsor time and money.

Quality Agreements are an effective bridge to a successful future for companies in the pharmaceutical and biopharmaceutical industries.

References

1. EU GMP Guide Part I, chapter 7, and ICH Q7 Guideline, chapter 16; CH Q10 Guideline, chapter 2.7, ICH E6 (R2)

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Gloria Miller has worked for Premier Research since July 2011 with increasing roles of responsibility from a Senior Auditor, QA Manager, and Associate Director, Quality Assurance, Risk, & Compliance (QARC). Gloria provides quality assurance leadership and support, liaising with the Senior Director of QARC, trains, mentors, evaluates auditing staff and deputizes for Senior Director, QARC as needed. She performs auditing and quality assurance activities in order to ensure that the systems, processes, and performance of Premier Research comply with applicable laws, regulations, Standard Operating Procedures, protocols, guidelines, and meet Sponsor and Premier Research requirements. Her duties include routine and directed site audits, GxP audits, vendor audits, system and process audits, database audits, computer systems validations audits, hosting sponsor audits, and providing consultancy services.

Gloria earned a Bachelor of Science degree in Chemistry in May 1988 from Meredith College in Raleigh, NC. She earned and maintains certification with the American Society for Quality (ASQ) as a Certified Quality Auditor (2006 to present). She earned and maintains regulatory affairs certification (RAC-US) from 2004 to present with the Regulatory Affairs Professional Society. Gloria earned certification as a Field Trainer and Targeted Selection Interviewer in 2009 at PPD. Active professional organization memberships include DIA, ASQ, and RAPs. She has presented papers at the RAPS Annual Conferences in 2009, 2011, 2014, and 2016 Regulatory Convergence Symposia. She presented papers at the 2014 annual DIA conference in San Diego as well as posters at the annual DIA conferences in Copenhagen and Philadelphia in 2012. Gloria also presented at the 2017 SOCRA conference in Orlando.

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