Implementing Quality Agreements at the Contract Laboratory

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The quality agreement (QAG) between a pharmaceutical company and its partnering contract research organization (CRO) is essential. This discussion outlines the elements of a useful quality agreement. It provides details of a simple procedure that the CRO can use to ensure that the terms of the quality agreement are implemented.

INTRODUCTION

A contract research organization (CRO) providing experimental testing services under current good manufacturing practices (cGMP) can expect to enter into numerous quality agreements (QAG) with pharmaceutical industry clients (sponsors). These agreements, usually initiated by the client, are intended to ensure that the CRO addresses key client concerns according to client requirements. For example, concerns may include issues such as timely client notification for a confirmed out-of-specification (OOS) result. More generally, the CRO must support promises made by the client to a regulatory agency. These typically will not appear in the master service (business) agreement between the client and CRO, but will appear in the QAG. The contract testing lab is, in effect, an extension of the sponsor's internal quality control (QC) lab. The contract lab also has the responsibility to ensure safety, purity, identity, efficacy, and potency of the product regulated by the US Food and Drug Administration. Having a good QAG in place, though important, is only half the battle. The CRO must also have approved procedures and practices to ensure adequate implementation. Previous published papers on this topic relate to QAGs from the point of view of the "contract giver" or sponsor (1). Each CRO ("contract acceptor") will implement the QAG in a unique way. This paper describes a simple approach to these agreements from the perspective of the CRO that has been successfully implemented.

CONTENT OF THE QUALITY AGREEMENT

A good QAG must be a suitable agreement and follow the general principles of any suitable agreement. A number of key elements are listed in Table I. These are also detailed elsewhere (2).

A good QAG should be a good fit to the quality program and quality systems at the CRO. The "goodness of fit" can be measured qualitatively and quickly by how well the QAG matches the quality manual of the CRO, particularly in the "Responsibilities" section. This section of the QAG provides details on client requirements to be in compliance with the cGMPs/good laboratory practice (GLPs) for work done at the CRO. For example, the CRO must have written job descriptions for positions responsible for cGMP-related activities at the CRO. Also, the CRO is responsible for having written procedures and schedules for the calibration and preventative maintenance of instruments and equipment at the CRO used to support the client's cGMP study.

It is common for the client to require notification of problems in an FDA inspection involving documentation or data belonging to the client. Although the frequency of occurrence of either of these cases is low, their criticality makes them high risk.

Another high-risk topic is change management. Not all changes are foreseen. Some changes may dramatically affect the CROs ability to meet the terms

TABLE I: Typical QAG content (for a contract testing lab).

QAG COMMON DETAILS
Scope: Specifies the products and services to be provided
Other agreements: What to do in the event that other agreements are already in place
Amend/terminate QAG: How to amend or terminate the agreement
Assignment: The CRO shall not assign any or all of its rights or obligations without the client's written consent, which may be granted or withheld at the client's sole discretion
Debarment: No individual or the CRO itself has been debarred or has been convicted of a crime for which it could be debarred pursuant to the *Federal Food, Drug, and Cosmetic Act*
Right to audit: Client shall have the right to audit the CRO's facilities and systems with regard to the products and services being provided
Responsibilities: Detailed listing of who is responsible to do what and includes both parties
Use of third party labs/contractors: Written consent from client is usually required
CLIENT-SPECIFIC DETAILS
Client notifications and approvals: Critical issues that trigger notification of the client and/or the client's approval
Resolution of quality issues: Protocol for dispute resolution
Investigations: Client-specific and regulatory requirements to be met by the CROs program
Deviations management: Client-specific and regulatory requirements to be met by the CRO
Out-of-specifications (OOS): Client-specific and regulatory requirements to be met by the CRO
Change management: Client-specific and regulatory requirements to be met by the CRO
Analytical methods and standards: Details on how the client and CRO lab will transfer analytical methods, who will approve methods and who (the client or the CRO) will provide the analytical standards to be used
FDA inspections: The client will typically want to be notified immediately of any FDA inspection of work done at the CRO for the client. The client will be very specific about how and when notification is required

of the QAG. Examples are downsizing or relocation of the CRO. The use of third party labs or other contractors creates more risk since these are further removed from the client control. Clients must rely on the diligence of the CRO to perform an adequate vendor qualification and to continually review work by the third party as critically as they review their own work. Often times, the volume, frequency, dollar value, and risk of noncompliance associated with the work being outsourced by the CRO to the third party will not justify a second QAG.

There are cases where the QAG can be created from a template and made effective with only slight modifications. The larger pharmaceutical company will "think global" in creating such templates (3). Doing so can be very cost effective, strategic, and timely since the basic QAG is created only once and may be quickly implemented. It will also minimize problems stemming from differences encountered at regulatory boundaries around the world.

IMPORTANCE OF THE QUALITY AGREEMENT

The QAG is a vital document with far reaching implications. Meeting the terms of the agreement is a responsibility of the quality assurance (QA) function at both the CRO and the sponsor organization.

Regulations

In the European Union (EU), having the quality agreement (also called "technical agreement") in place prior

TABLE II: QAG in the early project timeline.

1.	Establish a non-disclosure, non-compete agreement between the client and CRO
2.	Hold project meetings to discuss the client's project needs, CRO lab capabilities, CRO capacity and level of expertise
3.	Work out pricing and other details of the business agreement
4.	Make decision to contract with the CRO for services
5.	Complete the qualification of the CRO, including conducting the qualification audit and following-up on any/all audit findings (6)
6.	Approve the quality agreement (QAG) (This is often much earlier in the process such as at the time work is anticipated for the CRO. Timing may vary from client to client. It should be done before steps 7 and 8 below.)
7.	Train at the CRO on the QAG
8.	Send samples and schedule the laboratory work

to contracting the service or process is a regulatory requirement (4). Though not yet regulated in the United States, QAG are increasing used and expected (5).

Business Development

The QAG has its place in the business development and relationship development process. Achieving a good agreement in place with relative ease is a good indication that other business will develop smoothly. Proactive work done in drafting and approving the QAG may save time and money and prevent future discontent between organizations. The QAG has its place in the negotiation process to get large projects started and implementing the master service agreement for the project. There are costs and timelines associated with finalizing the QAG that cannot be neglected.

Project Timeline

A typical project timeline sequence is shown in Table II. The earlier that a QAG is implemented, the less the delay it will cause in the project timeline. It is not uncommon for the review and approval process to be simultaneous to the qualification audit. Other sequences are common. For example, some like to append the QAG to the master service agreement. A benefit to this approach is that the QAG will almost certainly receive a legal review. On the other hand, it may delay approval of the master service agreement, because the appended QAG will almost certainly receive a legal review!

Documentation

The quality agreement has its place among important controlled documents in the CRO. A partial listing of such documents that provide guidance and detailed written instructions for the conduct of the experimental study/lab work is provided in Table III.

Quality Systems

The QAG typically addresses compliance at the quality systems level. Quality systems such as change control, investigations, and metrology (instrument qualification and calibration) are designed to be comprehensive and address individual client or project needs. These are applicable to all projects in the same way as standard operating procedures (SOPs) governing day-to-day laboratory operations. In this way, a client may have several and diverse projects ongoing with the CRO all subject to a single QAG.

The client (sponsor) may have unique requirements. For example, they may want approval privilege on certain documents such as analytical test methods and laboratory investigations. Additionally, all clients will want the right to inspect the facility and audit the work being done in the lab. They will require immediate notification from the CRO if any of their projects become part of an FDA inspection. Because these requirements are not typically covered in documents such as protocols, methods, or SOPs, they are inserted in the QAG. The QAG is tailored to the specific needs of the client.

TABLE III: Controlled documents in the contract testing lab.

DOCUMENT NAME	ACTIVITY	DESCRIPTION
Quality agreement (QAG)	Specific to client	The QAG requires client and CRO approval and is controlled by the client ("contract giver").
Protocol	Specific to client and often specific to the project	The protocol typically requires both client and CRO to approve and is controlled by the CRO ("contract acceptor") or client depending on authorship. The protocol provides details of the experimental study (or validation) design and specifications and may contain detailed instructions for the laboratory to execute, including how to report data. Protocols often reference analytical test method and SOP documents.
Test method–Analytical or bioanalytical	May be specific to the client	The method may or may not require client approval and is controlled by the CRO or client, depending on who authored it. The method provides detailed instructions to the analyst in order to complete the analysis.
Standard operating procedure (SOP)	Not client-specific	SOPs do not require client approval and are controlled by the CRO. Laboratory and QA SOPs define the daily activities of the lab and QA unit to keep the lab in compliance with cGMP and GLP regulations.

QAG and Other Document Changes

Controlled documents cannot be changed without creating a new version and receiving a review and approval by either the original approvers or those at the same level of knowledge and authority. Such documents typically undergo periodic (often annual or biannual) review, revision, and approval. It is common to annotate on a "justification for changes" or "history of changes" page the changes that were made and the justifications for these changes. Along with being controlled, the QAG is a confidential document and must be treated appropriately.

A SIMPLE WAY TO IMPLEMENT THE QAG

Several key elements are critical for the CRO implementation of the QAG. Management and QA must have proper respect for the QAG and give it the priority it deserves.

QAG SOP

The QAG must be part of the CRO quality program. The CRO should have an established SOP of QAG approved by management and QA. A stepwise SOP describing the implementation of the QAG facilitates determination of non-compliance. It also facilitates communication to lab personnel and principal investigators the essential terms of the QAG. These QAG SOPs can form a good basis for training and can define how the CRO will deal with revisions in the QAG.

"Buy-In"

Another key element is "buy-in." The CRO must work through all of its terms and determine how each can be accommodated by the quality systems before approving the agreement. If there are weak spots in either the quality program or the QAG, these must be remedied.

Communication

Clear communication of QAG requirements is essential. For example, the QAG may be condensed to the most essential 10 bullet points in simple language. These points are then posted in plain sight in training rooms. The owner of the agreement is identified only by client code so as to protect client confidentiality. Further detailed communication on the QAG is achieved via the QAG SOP.

Training

Before starting any laboratory project, the principal investigator (PI) or study director holds a kick-off meeting with all participating scientists and at

least one member of the QA unit. The purpose of the meeting is to review the study protocol, analytical test methods, safety issues, and other aspects to ensure project readiness for initiating the project. The PI will review the key elements of the QAG with the project team. The PI uses a checklist to ensure all topics have been covered in the meeting. This checklist is signed and dated by the PI and all in attendance, and maintained by the document control unit with exact copies going into each attendees training file. Training on the QAG SOP is completed through the SOP training program in place at the CRO.

Monitoring

QA will monitor QAG deviations. Any deviation is addressed through the CROs corrective and preventative action (CAPA) program. Determining the most likely causes for failure of the CRO lab to adhere to the QAG leads to simple preventive actions. CRO QA unit and laboratory management carefully reviewing the draft QAG should identify potential deviations. These will include obstacles such as unclear wording, inconsistencies or contradictions, and unrealistic requirements. Any deviation from the QAG should require an investigation. An investigation requires an investigation report and an impact assessment. QA and management will review the impact assessment and the deviation through the CAPA program. Ultimately the investigation report should have a QA follow-up and be approved by the CRO QA, management, and the client. Some clients may have specific deviation requirements that are defined in the QAG.

Follow-up

Once the CAPA actions have been approved, QA will perform an effectiveness check to confirm that the actions taken have prevented another occurrence of the deviation.

SUMMARY

A sponsor enters into a QAG with the expectation that the terms will be fully implemented throughout the life of the agreement. The procedure for ensuring that the CRO implements the QAG is based upon communication and training: specifically, adequate communication to, and training of, lab analysts, principal investigators, lab managers, and quality assurance auditors on the critical requirements imposed on the CRO by the quality agreement. Though this is not entirely a novel approach, it is straightforward and effective. Having a good QAG in place does not eliminate the need to audit the CRO. The audit of the CRO should include a verification check that key personnel are aware of the terms of the QAG and that the CRO is implementing the agreement.

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