Implementing an Effective Provider Qualification Program at the Contract Laboratory

Richard C. Wedlich , Agata E. Libera, Joseph M. Fransen, Eric Sadosky, Matthew T. Therrien, and Kevin J. Webb

Abstract

This paper is intended to provide useful hands-on guidance regarding the process of provider qualification. What we have learned of this comes mostly from being employed in smaller contract research organizations (CROs) that have been focused on providing good manufacturing practices (GMP) and good laboratory practices (GLP) support to major pharmaceutical and medical device manufacturers in the form of specialized contract analytical testing services. While this niche is small in comparison to manufacturing, it is clearly within the purview of the US Food and Drug Administration that monitors and holds it to standards in common with manufacturing. The objective for the lab is to design and implement a program that meets all applicable regulatory requirements, not demand too many company resources and correctly place the providers. The approach taken is risk-based. The program design must integrate well with the laboratory's other quality systems. We cannot claim to be the originators of these ideas; rather, this paper takes from many suggestions made by many quality assurance (QA) auditors over many years having the task of qualifying our laboratory.

Introduction

The provider selected to support a GMP or GLP programs is, from a regulatory viewpoint, "part-and-parcel" to the operation (1). Those GMP and GLP requirements imposed upon an organization in order to ensure the quality, integrity, identity, purity, and/or strength of the product pass through to the provider.

The only way to show the regulatory agency that we take responsibility for the provider's service or product (i.e., "work" contracted or purchased) is to perform and document a qualification of the provider. Our approach typically includes an audit (facility-based on-site assessment) followed by a periodic quality review of their work and requalification. The qualification audit might focus on the quality systems that are in place at the provider's facility to ensure the provider can meet regulatory requirements. It might include verification that the CRO can perform the requested testing by asking them to complete "qualification trials" performed on standards or "knowns" before considering them qualified to perform testing to support a GMP or GLP study. Manufacturers of drug products and medical devices have, over many years, developed vendor and supplier qualification programs intended to ensure that products and services they purchase are "fit for intended use or purpose." Even so, with economic globalization come challenges that even the world's most reputable companies must face anew. As they outsource to smaller companies (i.e., providers), they recognize that the chain is only as strong as the weakest link (2). FDA Warning Letters abound containing observations such as "Your firm failed to properly evaluate a contract laboratory to ensure GMP compliance of operations occurring at the contract site……Although you have agreements with other firms that may delineate specific responsibilities to each party, you are ultimately responsible for the quality of your products and the reliability of test results."(3). Most quality agreements (QAG) between the contract-giver and contract-receiver will contain

Richard C. Wedlich , Agata E. Libera, Joseph M. Fransen, Eric Sadosky, Matthew T. Therrien, and Kevin J. Webb

a "right to audit" section. This section details the organization's expectations allowance to enforce the terms of the agreement and perform regular (on-site) audits (4). Vendor and supplier, or more generally, "provider" qualification is, and will continue to be, a hot topic appearing frequently in FDA inspections of contract laboratories.

Scope and Methods

All CROs, regardless of size, rely upon a large number of providers. All of these should be considered as falling under the scope of the provider qualification program. At first, this may appear a daunting task owing to the number and diversity of providers: pest control, janitorial services, chemical reagents, reference standards suppliers, instrument service providers, calibration services, archival services, facility services (e.g., electrical and HVAC), stability storage, computer software suppliers, third party auditors, consultants, and providers of data to support GMP and or GLP studies to name a few. While our focus tends to be on laboratories, the concepts presented here apply to the qualification of all contract service providers.

It is convenient to group providers and develop a qualification strategy that works for each group (i.e., domain). This eliminates the need to write a general procedure to fit all, which is nearly impossible to do. The defining properties of each domain, once identified, will lead to an understanding of 1) the proper procedures to qualify members of the domain and 2) the proper "risk" (defined later) to assign to the provider in the domain. Accepting "very low risk" as one possible assignment allows the program to be comprehensive and flexible without overburdening it.

A list of domains we use is provided in Table I. As a rule of thumb, providers are lumped by considering how "close to the data" they are. This is clarified with an example: contract labs providing GLP/GMP data such as the results from an analysis on a test article or client sample are as "close to the data" as one can get and define a domain into which we also place those that "manipulate" or handle data, including providers of data archival services and providers of software intended to handle data. The boundaries between domains are admittedly rather arbitrary. Still, the domains chosen should be indicative what "you are trying to guard against," which in our case is the adulteration or loss of

the GMP and/or GLP data that we report to our clients.

Domains are also convenient for sorting out the methods potentially used for qualification. For example, the mail audit questionnaire used to qualify a GMP contract lab is typically inappropriate for qualifying a provider of metrology services, so it makes sense to place these providers into different domains. While qualification procedures and risk assignments may vary from domain to domain, the provider qualification program will recognize the similarities among domains and treat them all the same way. We do this by developing and implementing a master plan standard operating procedure (SOP) while simultaneously developing and implementing domain-specific, specialized SOPs. For example, procedures for program administration, quality monitoring, and record keeping are in the master plan that, for conducting a mail audit of a contract lab, is in the appropriate domain-specific SOP.

Process Maps

Provider qualification is a process or collection of processes that interface with a number of quality systems in the organization. It therefore relies upon a diverse work pool and "extends into the white spaces of the organization chart" (5). For example, any disqualification procedure should be based on the provider's failure to respond appropriately to a corrective action report issued by your QA group and documented using your corrective and preventive action (CAPA) quality system. It will necessitate a decision from management to seek out another source and require the requestor of the service/material to do so. It might also necessitate an investigation involving the principal investigator, analysts, client, and others.

It is useful to map out the process. Typical map designs include using a train of boxcars where the process is the train and each boxcar is a major activity and use of a flowchart. The process map is a good way of showing key roles and responsibilities. Also, key documentation and approvals needed along the process as well as start, end, and in-process benchmarks can be mapped. Process controls such as documentation and approvals are typically inserted at the links between critical activities and may represent specifications to be met, points for monitoring and self-improvement, bottlenecks, delays, and expenses. A rough example of

Table I: Domains for the Contract Lab to Consider in Organizing a Provider Qualification Program.

Domain	Examples	Risk
Direct Impact	• Providers of GMP and/or GLP experimental (test) data • Data archival services • Computer software for manipulation/storage of data • Stability storage providers	High
Indirect Impact	• Providers of metrology-based services such as those who install, qualify, and perform PM and repair instrumentation or equipment	Moderate
Indirect Impact	• Providers of computer software not specific to data analysis and storage and IT services	Moderate
Indirect Impact	• Providers of materials such as reference standards, chemical reagents, and solvents and purified gases used in the GMP and/or GLP lab	Moderate
Little Impact	• Providers of facility-based services such as pest control, waste management, HVAC, janitorial, laundry, electrical, plumbing, etc.	Low
No Impact	• Providers of experimental (test) data generated intentionally under non-regulated (non-GMP and non-GLP) laboratory conditions (e.g., analytical method optimization data prior to GMP method validation) • Providers of materials not used to support GMP and/or GLP work	Very Low

(Note: The list is not meant to be all-inclusive but rather suggestive. By "impact," it is meant "impact on the quality and integrity of the experimental GMP and/or GLP data")

a process map in the form of a flowchart is given in the Figure for the qualification of a provider.

The qualification process does not end once the provider has been qualified and placed onto the approved provider list. QA will assign a requalification date. For some domains, it is a good idea to work out a QAG with the provider prior to the qualification audit. During the audit, the auditor can verify that the provider has the means to meet the terms of the QAG. Often, however, the client will not make the effort to initiate the QAG without first ensuring that the provider is qualified. Also, the QAG details how specific aspects of the work are to be done, and since the provider must first be qualified to do the work, QAG checks are made after the work is in progress. QA must monitor the services performed/materials provided throughout the qualification period. The program must provide the means for 1) following up on complaints received about the provider's goods or services, 2) assuring CAPAs are taken by the provider and reported by QA, 3) rejection and quarantine of materials deemed adulterated, and 4) disqualification of the provider.

Risk Management
In assigning a risk level to a provider, we assess both the likelihood and severity of a non-compliance or other

quality issue (e.g., complaint) stemming from the use of that provider for the particular service and/or type of material we are asking them to provide. The risk matrix (likelihood vs. severity) is therefore *pre-defined* before any steps to qualify the provider are taken and certainly before any outcome is determined as to whether or not the provider should be deemed "qualified." The risk assignment determines the extent of the qualification (i.e., how much time and money will be spent on it, how long it will take to complete, and what procedures will be followed to perform it). A provider is deemed "qualified" when we have determined and documented that they are "fit for our intended use." A variety of methods that employed to qualify providers are listed in Table II.

Risk levels used are very low, low, moderate, and high. As an example, a very low risk assignment might be given to the laundry service that cleans lab-coats. Providers may provide multiple services or types of materials, and a risk assignment is made for each. For example, under one contract, the contract lab may be providing research and development (R&D) data that are not intended to be generated following strict adherence to GMP lab conditions while under another they are providing GMP data. The risk assignment

Richard C. Wedlich , Agata E. Libera, Joseph M. Fransen, Eric Sadosky, Matthew T. Therrien, and Kevin J. Webb

Figure: Example Flowchart (QA for Quality Assurance and DCU for Document Control Unit) Showing One Time Through the Loop for Qualification of a Provider.
(Note: There is actually no end to this process, since periodic requalification is required)
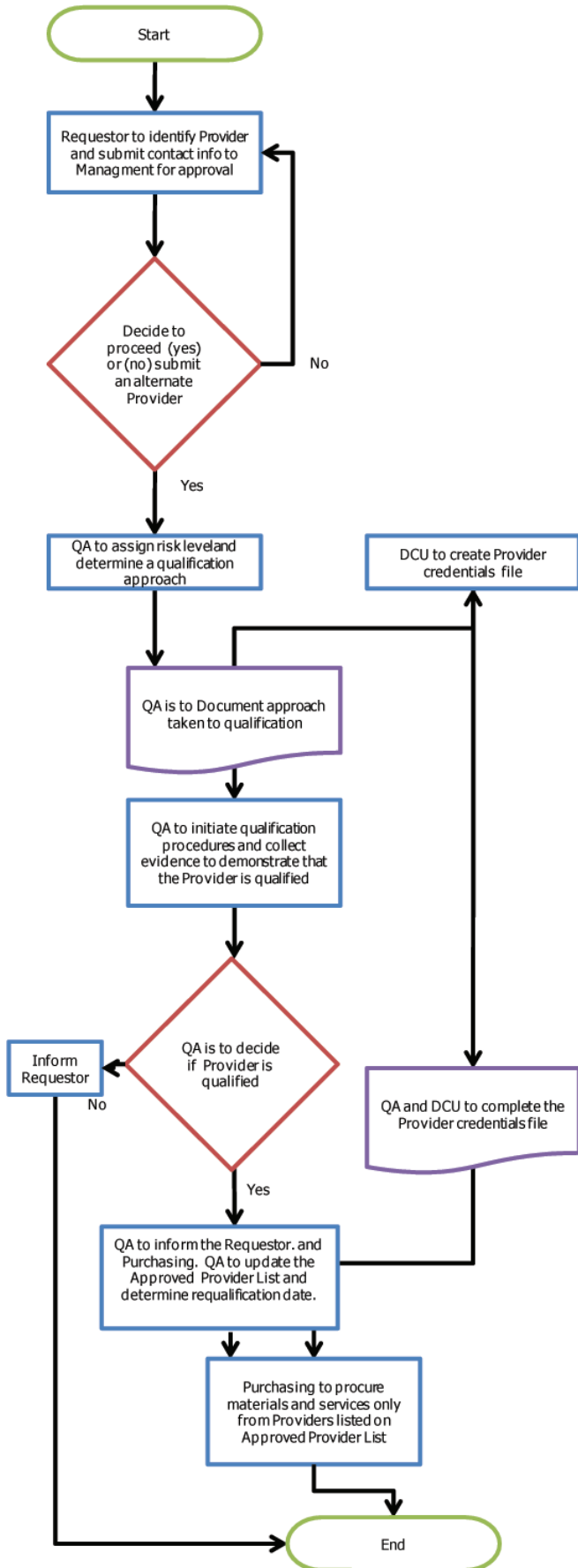
can be adjusted. For example, a pest-control service provider may be considered low-risk because there is no inherent problem with pests at the facility but be raised to a higher risk level should the pest concern grow. The pest risk depends upon many factors, including geographical location, climate, and type of operation (e.g., production vs. laboratory), which may all impact upon the likelihood of having pests and your tolerance level, which impacts upon the severity of the problem.

A provider that falls into the high-risk category will typically be qualified by conducting a mail audit (a copy of the most recent FDA Establishment Inspection Report [EIR], if applicable, should be attached) pursuant to conducting a facility audit using either NSF Pharmalytica auditors, a third party auditor, or a combination of both. A provider of a chemical reagent that falls into a low risk category may be qualified based on past direct personal experience using the provider and the provider's reputation in the industry. One outcome of the qualification process is the assignment of one of the following classifications to the provider: Approved, Conditional, or Not Approved. The classification does not extend beyond the qualification meaning that it is limited to what is being deemed as "fit for use."

Risk should be lowered/managed by 1) careful selection of the provider, 2) proper qualification, 3) diligent monitoring of the product or service over the lifecycle, 4) implementing change control procedures via the QAG, 5) writing good in-house standard operating procedures (SOPs) for conducting the provider qualification and managing and administering the qualification program, 6) providing training internally on the written procedures, 7) establishing good quality systems in your own lab that interface well with the qualification program, 8) using "common wisdom" such as expecting a lot from yourself if you are going to expect a lot from others, and 10) developing good relationships with your providers.

Consider the following as an example of cost-effectively lowering the risk of outsourcing by leveraging your own lab's strong GMP/GLP program. A lab that has a strong program will have quality systems and practices in place serving to lower the risk of using a provider of material (e.g., reagent, solvent, standard) that ships with a lot-specific certificate-of-analysis that

Table II: Common Considerations Used by the Qualification Team to Evaluate Provider Qualifications.

1	Past direct or personal experience using the provider
2	Provider's reputation in the industry
3	Provider's website and capabilities and expertise claims
4	Professional references submitted by the provider
5	Relevant certifications (e.g., International Organization for Standardization (ISO) certifications, lab accreditations), licenses, etc.
6	Dunn & Bradstreet financial review of the firm to assess the provider's commercial viability; this may be a critical concern; for example, if the provider is to be relied on to provide stability storage for extended times (e.g., years).
7	Information available through the *Freedom of Information Act* helping to establish the quality history of the firm, such as the FDA EIR and debarment history
8	The provider's quality manual
9	A mail audit using a well-designed quality questionnaire
10	A facility (on-site) audit or a qualified third party audit or assistance in the audit preparation and conduct.

is generated by the provider. These include 1) proper use of experimental "blanks," 2) use of analytical system suitability testing/requirements, 3) having a strong out-of-specification (OOS) investigation program in place, 4) employing point-of-use checks, 5) documenting in the experimental record the lot number used, and 6) making routine checks on materials receipt and storage. Combined, these may eliminate the need to spend a lot of time and money qualifying the material so that the focus is on qualifying the provider in order to establish "quality at the source" (6). Any materials identified as OOS or otherwise deemed adulterated are removed to quarantine storage, and the provider, depending on corrective action taken, may ultimately be disqualified. As another example, consider equipment and instrumentation installed and qualified by a metrology-based provider and intended to provide GMP/GLP data. Although you would qualify such a provider, the risk is further lowered by requiring regularly-scheduled (e.g., "day of use") performance checks be conducted on the equipment or instrumentation.

Written Procedures (SOPs)

Use of SOPs is one important way to control and reduce risk. There are, of course, other, non-procedural ways such as so-called "engineering controls" that are based on strong cause-and-effect relationships (e.g., testing). SOPs work well when the "process elements" are people and the compliance world thinks in terms of SOPs. Having the correct set of SOPs in place, a management team to enforce them, and using the QA group to check

that they are being followed establishes the required control. SOPs are an excellent vehicle for training employees using the provider qualification program and play a large role in the continuous improvement of the program. Each organization must write its own qualification program SOPs. They will match well with key roles and responsibilities and with the process maps. They must form a clear path to the goal of the qualification program.

Administering The Program

"Strategies do not fail when they are being analyzed or when the objectives are being set. They fail during implementation and, more particularly, due to the lack of proper project management." (7). Once in place, the biggest challenge posed by the provider qualification program at the small CRO is its administration, and this becomes even more apparent within a large CRO. How a CRO handles this challenge is a test of how well the company is vertically integrated. A non-exhaustive list of things to consider follows:

- Give careful consideration when identifying potential providers for qualification (8).
- Keep the number of qualified providers to an optimal minimum.
- Put enough controls into place and in the right places.
- Consider using a process control spreadsheet.
- Train personnel on written procedures, including the quality agreement.
- Review and revise: "If processes are not continually

Richard C. Wedlich , Agata E. Libera, Joseph M. Fransen, Eric Sadosky, Matthew T. Therrien, and Kevin J. Webb

and incrementally adjusted and improved, they naturally deteriorate to a point where they stop functioning."(9).

- Take a risk-based approach, and use risk management tools including a strong change-control program.
- Understand that having more details in the process map allows for more control but also makes for a more labor-intensive/expensive program to administer. It can also increase the risk of non-compliance by "promising too much." It is necessary to establish an optimal program and this may require a couple of iterations.
- Understand that provider qualification is not a task; it's a program.
- Do not forget your client or your provider when you stand in between them. Establish a good quality history with both.

As an example of the third item (a control measure), consider at the purchasing level to include a drop-down menu of approved suppliers on your electronic purchase order from which to select the provider. Should the requestor prompt purchasing to buy materials from a supplier not on the approved provider list, the request would be returned and the requestor would either ask QA to initiate a provider qualification or would seek another provider. Considering the fourth bullet (process control spreadsheet), this may be a simple electronic spreadsheet that mates with the process map and be used to track/monitor key process parameters such as the provider qualification status and requalification due date. An example of the seventh bullet (a risk management tool) is the quality QAG. Another is the process map.

Summary

The goal is ultimately to gain competitive advantage through the management of the supply chain thus reducing the risk (cost) of a non-compliance with, for example, GLP/GMP regulations, quality specifications, client expectations, or some combination of these. In order to do this, provider qualifications must be meaningful, timely, well-documented, and risk-based. Having a well thought-out plan for the qualification program from the start helps ensure that the program integrates with the other quality systems

in the organization and thereby reduces the cost of maintaining the program while increasing its chance for success.

References

1. B. Frey, "Supplier Management," published on *IVT Network*.
2. R.E. Cole, "What Really Happened to Toyota?", *MIT Sloan Management Review* **52** (4), 29-35, 2011.
3. FDA Warning Letter WL 11-09 dated Jan. 20, 2011.
4. R.C. Wedlich and K.J. Webb, "Implementing Quality Agreements at the Contract Laboratory," *Journal of GXP Compliance* **16** (4), 54-58, 2012.
5. G. Rummler and A. Brache, *Improving Performance: How to Manage the White Space on the Organisation Chart*, Jossey-Bass, San Francisco, CA, 1995.
6. D.M. Stephon, "Establishing a Supplier Qualification Program," *Journal of GXP Compliance* **6**, 2002.
7. A.P. Van Der Merwe, "Project management and business development: integrating strategy, structure, processes and projects," *International Journal of Project Management* **20**, 401-411, 2002.
8. D. Jenke, "Insights Gained into the Identification, Qualification and Utilization of CRO Laboratories in Extractables and Leachables Studies," *Pharmaceutical Outsourcing: The Journal of Pharmaceutical and Biopharmaceutical Contract Services*, posted March 27, 2013, available at: http://www.pharmaoutsourcing.com/Featured-Articles).
9. Ibid (7). **GXP**

About the Authors
Mr. Richard C. Wedlich is Director of Quality Assurance. He may be reached by email at rwedlich@nsf.org. Ms. Agata E. Libera is Quality Assurance Auditor. She may be reached by email at alibera@nsf.org. Mr. Joseph M. Fransen is Quality Assurance Auditor. He may be reached by email at jfransen@nsf.org. Mr. Eric Sadosky is Metrologist. He may be reached by email at esadosky@nsf.org. Mr. Matthew T. Therrien is Operations Manager. He may be reached by email at mtherrien@nsf.org. Mr. Kevin J. Webb is Program Manager. He may be reached by email at kwebb@nsf.org. All authors are from NSF Pharmalytica, a part of NSF Health Sciences.