Facilitating Client Audits

The Contract Laboratory Perspective

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Pharmaceutical companies rely on outsourcing organizations that anticipate and prepare for client audits. Such contractor companies become collaborative partners. A technically proficient contract organization understands client needs, knows the regulatory environment in which drug development takes place, and sees a client audit as a professional opportunity to show its expertise. (This article was previously published in *BioPharm*, 15 [7], 12–16 [2002]).

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Pharmaceutical companies continually face the challenge of increasing their speed-to-market for new drug products. As a result, many pharmaceutical companies now outsource analytical development activities to contract laboratories to accelerate the process. Compliance audits are a critical step in initiating and managing outsourcing processes because they help verify that the contract laboratory can perform the specified work in a technically proficient and regulatory-compliant manner. An audit is also an excellent opportunity for pharmaceutical companies to communicate specific performance expectations. Audits allow the contract laboratory to educate the client about the systems and procedures that will be used to support the outsourced analytical projects. Contract laboratories are responsible for having well-designed systems and procedures in place to support client audits and to provide audit follow-up that meets client needs. A successful audit can be the start of a positive outsourcing relationship.

Outsourcing is thriving

Revenue for publicly traded contract organizations grew more than 20% in 2001 (1). Research and development budgets at large pharmaceutical companies are expected to expand between 8 and 10% this year: Twenty to 30% of that is expected to be outsourced. Although large pharmaceutical companies have traditionally been the primary clients for outsourcing companies, smaller pharmaceutical and biotechnology com-

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panies are anticipated to be a growing source of revenue for contract organizations (2). Thus, outsourcing will continue to play a major role in drug development strategies. Furthermore, contract laboratory audits will continue to be a critical activity for developing and maintaining outsourcing relationships.

Initiating the relationship. Typically, clients initiate outsourcing relationships with a site visit to assess due diligence issues such as capacity and technical capability and to discuss technical project details. Joe Albanese, associate director of quality assurance at Johnson & Johnson (www.jnj.com), says, "We audit for both business and compliance reasons." Compliance audits are usually performed after companies have assessed the contract laboratory from a business perspective and determined that it meets their outsourcing needs. This timing does not diminish the importance of the compliance audit in the outsourcing process because clients can still choose not to pursue the relationship if the compliance audit does not confirm their initial due diligence assessment.

Albanese adds that compliance audits are "mandatory per our standard operating procedures [SOPs], and we will not use a contract research organization without auditing them. We have standards that must be met." Clients also conduct periodic compliance audits to review projects in progress at the contract laboratory.

Typical preaudit questionnaire sent to client

Typical questions that contract laboratories send to clients before a client audit might look like this.

Preaudit Questionnaire

1. Is this a GLP audit? (check one): ❑ yes ❑ no
2. How much time is anticipated for SOP review? _____
3. How many attendants will be participating? _____
   • Please provide name and title of each attendee (include consultants):
   _____
   _____
   _____
4. What is the purpose of this visit? (check all boxes that apply):
   ❑ First-time visit
   ❑ Annual GMP audit
   ❑ Visit targeted to specific studies
   ❑ Other. Please explain: _____
   _____
5. List projects to review, including compound name, protocol number, etc. _____
   _____
   _____
   _____
6. Are there specific aspects of the study you wish to discuss? (check one): ❑ yes ❑ no

   If yes, please detail:
   _____

Contractor responsibilities

Contract laboratories must follow three fundamental rules to successfully facilitate an ever-increasing number of client compliance audits.

- Develop and operate appropriate systems and procedures.
- Develop a culture among staff that supports client compliance audits.
- Understand the outsourcing factors of success: quality, timeliness, communication, and relationship (3).

As the pharmaceutical industry spends more on outsourcing to contract laboratories, those laboratories must have well-defined quality systems that provide cost-effective, compliant products. Their systems must be flexible so that they support each client's various needs, yet robust so that the laboratory maintains regulatory-compliant control over all projects.

Quality systems. Quality systems include written SOPs that address project obligations, analytical test methods, sample controls, metrology protocols for all facilities and equipment, data acquisition, data review and audits, and documentation and archival.

An audit culture. Successful contract organizations develop a corporate culture that supports client audits. Contract laboratory staff are trained to expect and participate in client audits, and they understand the importance of these audits to the outsourcing relationship. Successful contract organizations are frequently audited by both prospective and existing clients: The laboratorymight have audits almost every day. As a result, contract laboratory staff, including QA, document control, and laboratory personnel, among others, must understand that client representatives are on site, and that staff performance may be subject to critique by clients. Written procedures for hosting visitors during audits should designate responsibility for client interaction and can be used as training tools for staff members.

Because contract laboratories experience so many audits, they can offer pharmaceutical companies insight into the pulse of the industry, particularly about compliance issues. For example, out-of-specification (OOS) procedures are a key theme of most audits, and for a brief period before January 2000, Y2K vulnerability also was a key audit topic. Compliance with 21 *CFR* Part 11 for electronic records and electronic signatures is now a major topic and has become a focal point of most audits

(4). During audits, contract laboratories learn how various companies approach compliance topics, and they can use that knowledge to improve their own systems and procedures to ensure that work performed for clients complies with the most current industry standards.

Success factors. The third fundamental responsibility of contract laboratories is that they develop an understanding of key parameters that measure success in an outsourcing relationship: quality, timeliness, communication, and relationship (3). Successful client audits require all these parameters—factors built in by the collaboration of the contract laboratory and the client company. Albanese says, "We want to facilitate communication. We don't want to be surprised at the end of a study because we thought our needs were understood."

Preparing for the audit

Scheduling the audit, accurately determining the audit scope, and setting an audit agenda are important to effectively maximize the time and energies of all participants and to complete the audit thoroughly and satisfactorily. Typically, a contract laboratory will have a project manager work directly with the client to make necessary arrangements: setting an audit date and arrival time, identifying participants by name and title, and agreeing to the audit scope and agenda. Making these arrangements in advance ensures that all required personnel and documentation are available during the audit. A questionnaire, such as that in the "Typical preaudit questionnaire" sidebar, also can be sent to clients in advance of the audit to obtain information that allows the contract laboratory staff to better prepare and effectively support the audit.

Many clients also use a preaudit questionnaire to obtain routine information and specific details about a laboratory's operations to make optimum use of their time spent on-site conducting the audit. By providing such documents before an audit, clients allow contract laboratory staff the time to accurately complete and provide the requested information.

Audit agendas, usually set by the laboratory through discussion with the client, help keep a visit on track. The "Typical client audit agenda" sidebar shows that this tool can be used as a guide for visit expectations. Time is typically budgeted for presentations by the contract laboratory so that they can explain their quality systems and technical capabilities. Such presentations are an excellent opportunity for participants to begin developing the communication necessary to a successful relationship and for the client company to learn how the contract laboratory executes projects.

The systems used by a contract laboratory and those used by a client may have some differences because contract laboratories develop procedures that apply to many clients and projects, whereas the client company's system only supports its proprietary needs. Quality presentations offer clients answers to many of their audit questions and generate discussions that help clients in understanding how a contract laboratory executes its procedures. Contract laboratories learn from each audit, and clients have the opportunity to benefit from the lab's experience. Contract laboratories develop technical expertise that can prove useful to client companies. The audit facilitates discussions that may provide benefit to the client.

Typical Client Audit Agenda

Audit Agenda	
9:00	Welcome, introductions, agenda review
9:15	Company presentation
9:30	Technical presentation: Overview of technical capabilities, including the expertise and capabilities of scientific personnel, laboratory instruments, and facilities available
9:45	Quality assurance systems presentation: Overview of systems and procedures
10:45	Laboratory tour
12:00	Working lunch
12:30	Audit: SOP review, documentation and data review, and project discussions
4:00	Wrap up
4:30	Departure

Quality agreements between client companies and contract laboratories are a recent development in outsourcing. A quality agreement outlines the roles and responsibilities of both the client and the contract organization for quality aspects of the relationship. These agreements are typically time limited and periodically revised. Examples of routinely covered topics are highlighted in the "Quality agreements" sidebar.

Successful contract laboratories will have already addressed the topics listed in a Quality agreement as part of their quality systems and procedures. Once such an agreement is in place, compliance with its terms is typically a topic of future audits.

Conducting the audit

Regardless of the approach taken, the goal of a client audit is to obtain evidence that adequate quality systems and procedures are in place and are being followed by the contract laboratory. Audits usually begin with a brief introduction of the client audit team and contract laboratory representatives followed by a review of the agenda and the audit scope. Most auditors begin by reviewing organizational charts of the laboratory staff and documents about the regulatory history of the laboratory, its facility and size, and other general topics. Several auditing styles are used frequently. Some auditors use checklists. Others choose to follow the flow of an analytical project and review applicable documentation and controls for each process step. Some prefer to spend time reviewing SOPs before asking questions and reviewing associated documentation. And some clients prefer to begin with a laboratory tour. Experienced contract laboratory staff learn to recognize the chosen audit approach and adapt to the client audit team to assist it in completing its review.

Quality agreements

Quality agreements outline the roles and responsibilities of both the client and the contract organization. Topics typically found in a quality agreement include the following:

- Requirements that the contractor has all applicable licenses and registrations and will follow all applicable laws, rules, and regulations
- Agreements that the client has the right to audit the contract organization, given sufficient notice for scheduling
- Lists of roles and responsibilities for contractor record retention and disposition
- Requirements for client approval of key documents such as protocol and analytical test methods
- Statements that subcontracting will not occur without the approval of the client

Staff attending the audit. Contract laboratory hosts need an appropriately sized conference room reserved to accommodate the audit team and all the audit documentation brought in for review. Adequate space facilitates an orderly review of documentation, procedures, instrument calibration and qualification information, and training records. A set of SOPs should be available because review of those documents is a critical part of audits. Essential contract laboratory representatives who must be present during the audit include appropriately trained senior members of the quality group who can explain the systems and procedures. On the basis of the scope and audit agenda, other staff might be required during parts of the audit, including personnel from metrology, laboratory analysis, stability, IT, and sample coordination.

Document retrieval. Key contract laboratory staff typically not present in the room but who are critical to the success of the audit include members of the documentation group responsible for retrieving records requested during the audit. Personnel training, instrument qualification, calibration, and maintenance records are some of the documents reviewed during most client audits. Experienced contract laboratories should already have a good system of internal communication that facilitates expedient retrieval of any record or documentation that supports procedure reviews or that illustrates how systems are followed.

Clients will usually want to spend time reviewing specific SOPs during the audit. Examples of frequently reviewed key procedures include OOS investigations; instrument installation, operation, and performance qualification (IQ/OQ/PQ); sample control; and primary data recording. Initial compliance audits usually focus on the contract laboratory's use of its procedures to complete analytical projects. Periodic, follow-up audits review the accuracy of reported results compared with raw data and the level of compliance exercised while conducting the analytical study.

Laboratory tours. Laboratory tours that highlight specific areas such as sample control, stability, and document archives are a key part of every audit. Laboratory representatives facilitating the audit should be well versed in guiding an audit team through the facilities. The tour offers an opportunity to illustrate procedures—such as how reagents and samples are labeled and stored during use and how instrument calibration status is identified—and to review areas such as documentation archives and computer server rooms. The tour also demonstrates the laboratory's technical capabilities and capacity by highlighting the adequate space and equipment available to support a client's needs.

Audits typically conclude with a wrap-up meeting during which the auditors present and discuss any observations that require follow-up action by the contract laboratory. The wrap-up meeting is an excellent opportunity to begin collaborative communication between the two companies to constructively manage the outsourcing relationship. Although auditors typically issue a formal report at a later date, the representatives of the contract laboratory should carefully note any observations presented during the wrap-up meeting and make sure they understand the expected actions and timing for completing the response to those observations.

Follow-up to the audit

Audit reports from clients and written responses from contract laboratories are usually coordinated through a single contact to verify timely completion of responses and follow-up by the contract lab. The contact individual is typically a senior member of the contract laboratory's quality group. As mentioned, contract labs rely on input from many functional areas of their organizations during client audits. That same group approach is often useful for completing a written response and for coordinating follow-up activities.

The response from a contract laboratory is more than just a written reply to the audit. Responses to audit observations should clearly indicate actions to be taken to address each observation and an estimated date of completion for each action item. Additional communication such as follow-up conference calls can be useful tools for updating client companies about the status of actions completed and remaining. The response to an audit represents a commitment to the client, and compliance to the statements made in the response is a measure of a contract laboratory's performance in support of timeliness and quality.

Accelerating drug development

Client audits are an integral part of establishing and maintaining rewarding outsourcing relationships. Pharmaceutical companies increasingly outsource analytical activities to support accelerated drug development, but they must verify the compliance and technical capabilities of the contract laboratory they use. Understanding that need and successfully facilitating client audits are key responsibilities for contract laboratories.

References

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