How to Select a CMO

The 7 Steps of a Productive Quality Assurance Audit

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You've selected a Contract Manufacturing Organization (CMOs) to supply your drug candidate using criteria including budget, analytical capabilities, R&D, reputation for on-time delivery, solid project management capabilities and open communication. Now there's one more question left to ask: Does this CMO make good quality sense?

To answer this question, your quality assurance team or consultant(s) must audit the CMO's quality systems and manufacturing operations to ensure they meet your needs and are in compliance with current Good Manufacturing Practice (cGMP).

This article, part of our series on "How to Select a CMO," will discuss the steps involved in ensuring a productive quality assurance audit.

7 steps to a robust audit and site inspection of your CMO

1. **Do your homework**

   Learn about the FDA's current thinking on hot-button issues by reading pertinent Warning Letters posted on the agency's website, as well as the most recent FDA guidance for the industry. Look for trends. Search for any indication of the CMO's past regulatory history, including how it measures up to industry standards. With this information in hand, you will be better equipped to evaluate what you see when you arrive on site.

2. **Craft a full but flexible audit plan and agenda**

   If you request and review the CMO's quality manual and index of standard operating procedures (SOPs) in advance, you won't need to spend time on audit day deciding which documents to review. If you use a consultant to conduct the audit, insist on a pre-arranged plan to ensure the inspection will divulge all the things that are important for your project's success.

   Here is a typical PCI Synthesis audit agenda:

   (1) Introductions of the people doing the auditing, typically 1-2 people, 3 if representing a large pharmaceutical company.

(2) Overview of our company and business.

(3) Project review.

(4) Facility tour.

(5) Closeout meeting.

(6) Post-audit report and response.

Leave room on the audit agenda to pursue any items of concern you discover during the visit. You want to depart the site with enough information to make informed decisions about the CMO's readiness to perform your project.

3. **On audit day, don't spend a lot of time with Introductions and formalities**

   If you've done your homework, you already have a lot of the basic information about the CMO, its capabilities and its history. However, it's a good idea to spend time forming a good working rapport with your audit host. This includes making a clear statement of your expectations for the audit, and giving the host some knowledge of your background, experience and special interests. Take the lead in setting a cooperative tone for the meeting. Now you're ready to get to work!

4. **Begin your audit with a facility tour**

   Let your host know you will be taking your time looking around and asking questions. If time is at a premium, ask the host to streamline the tour by taking you through a mock process flow. Begin with the location where raw materials are received and sampled, through material testing and release, into the production area, and finally into final testing, storage and distribution. Along the way jot down some material lot numbers, names of personnel performing key tasks, and equipment identification so you can use them later as starting points for following a documentation trail. Take note of things that are unfamiliar, puzzling or just don't look right. Don't spend time with things that are obviously compliant. If one processing area is in good shape, move on to the next. That way, if you find something that requires a little digging, you will have ample time to make a thorough evaluation.

5. **Follow the basic approach of the FDA's system-based inspection program**

   Following the FDA's approach means you will always want to spend time reviewing the foundational quality systems such as Change Control, Deviations and Investigations, Corrective Actions and Preventive Actions (CAPAs), Out of Specification Investigations, and Training. A

convenient way to do that is by using the details --material lot numbers, names, equipment ID, etc. -- that you jotted down earlier, during the tour.

- For a specific material, ask your host to show you how specifications were set, and how the batch was tested and dispositioned.
- For personnel at work, ask your host to show you evidence they were trained on the tasks you observed them performing.
- For equipment, ask your host to show you original qualification, calibration and preventative maintenance records.

As you examine these documents, you will invariably touch upon many or all of the critical systems used to control and manage the CMO's resources.

6. **Do a thorough evaluation of documentation but don't spend all your time reading SOP's**
Pick a few of the CMO's high-level procedures. Ask yourself if they are too generic and lacking detail, or if they are overly detailed and complex. If the former, ask to see other examples of documents that may fill in information gaps. If overly detailed, ask for documented evidence that the CMO is actually performing all the requirements of the procedure. Don't get bogged down in assessing the nitty-gritty detail of any one procedure, unless your experience tells you something is fundamentally wrong. You're not there to edit their SOPs, but to make a judgement of whether the CMO is writing SOPs that comply with the regulations, and if the CMO is following its own procedures.

7. **Make meaningful observations/recommendations in your closing meeting and audit report**
Sit with members of the CMO's management and Quality Assurance staff for the closing meeting to review critical, major and minor observations. A knowledgeable and experienced auditor won't exasperate the host by focusing on the minutiae of a pet issue or by insisting on conforming the CMO's practices to one person's interpretation of cGMP tenets. Of course, if you have any serious concerns about the CMO's operation, don't hesitate to document them as a critical or major observation. Make sure to cite the specific regulatory requirement or guidance in your comments to avoid spending unproductive time on a mere difference of opinion. A worthy CMO's staff will welcome your input, provide an explanation and evidence for any observations they believe to be invalid, and make every effort to implement improvements based on the audit suggestions in your follow-up report.

Auditing is a great way for you to get a behind-the-scenes look at how your CMO operates. Conversely, it's also a great opportunity for your CMO to learn how others with different perspectives view their operation. Since no two audits are the same, an audit should be viewed as a learning opportunity for both sides. Be transparent and forthcoming. That is the best way to cultivate a helpful relationship with your CMO.

We have other articles about audits, including "Internal Auditing: A Sound Business Practice to Ensure Successful Project Outcomes in cGMP Manufacturing," as well as articles about questions to ask potential CMOs such as "10 Factors to Consider When Picking a Partner for Commercial Scale API Manufacturing" and "Key Questions To Ask Your CMO About Their Analytical Capabilities." Check out our blog for other related articles. Or to find out how to accelerate your API manufacturing project, call us at (978) 462-5555 or email us at info@pcisynthesis.com.