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You survived the FDA inspection. Now what? FDA always finishes the inspection by leaving you with a list of its observations. Part 3 concludes the survival guide series by describing the steps every company should take after the inspectors leave — from developing a corrective action plan to writing a detailed response document.

Survival Guide to FDA Inspections

Part 3, Responding to Observations

Responding to observations made by inspectors is often the most difficult part of completing the inspection process. But it is critical at this stage to remember the potential benefits that can result from an audit — better and more frequent employee training and more efficient operation, documentation, process improvements, and new scientific and technological advances. With these long-term benefits in mind, you and your team can tackle the postinspection process with energy and confidence. (For a quick review of Parts 1 and 2 in this series, see the “Reviews” box.)

The Last Day of the Audit

On the last day of the inspectors’ visit, executives are given an opportunity to defend the deficiencies cited by inspectors. Inspectors will listen to any defense offered by the management team before formally issuing the citations or the list of 483s (483 is the number assigned to the form that includes the citations found by FDA inspectors). During the process, avoid conflict, and do not become too emotionally involved. This is a second chance to present the facts objectively.

Use this opportunity to understand clearly what the citations are and what the inspectors intend to convey to you in the citation. Ask questions such as, “Do you mean that our procedures are inadequate?” and “Do you think we need more training in this area?” Responses to this type of question will help you clarify what the inspectors expect in remediation.

Developing a Response

Once the final observations have been issued, the clock begins to tick. FDA will expect a response within 10 to 15 working days.

Form a committee that includes, at minimum, members of the quality assurance (QA) and regulatory affairs departments. Put as many people on the committee as you like, but the best committee includes the

most qualified members of each department and maintains an environment in which topics can be discussed openly and decisions made easily.

It is the committee’s responsibility to review and clearly understand the observations made by FDA. The terminology can be confusing, so this is an excellent time to clear up any confusion and determine what needs to be done. It is also a chance to determine whether the observation is isolated or is the result of a bigger issue or trend that might be occurring.

Subcommittees. As the committee evaluates each observation, it should create subcommittees to investigate and respond to observations. Many times an investigation is the only way to discover why an observation was made. For instance, research and development might provide time and temperature specifications used for a drug recipe in the manufacturing process. If the time and temperature specifications are questioned during the inspection, and the manufacturing division never questioned those requirements, the investigation subcommittee will work with research and development to determine the rationale for developing the specifications in the first place and communicate it to all departments.

Response document. When developing a response, many companies make the mistake of writing general statements to address an observation. Responses such as “We will try harder next time” or “We will fix this SOP” are unacceptable. Responses should be as specific as possible. If there is more than one part to the observation, a separate response must be written for each section.

In each response, indicate whether the observation is an isolated incident or a global issue. For example, an inspector might notice a deficiency in the documentation process in which a validation package is lacking one specific element. It is the responsibility of the committee to

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Review of the Survival Guide to FDA Inspections, Parts 1 and 2

Part 1: Preparation Is the Key to Success (August 2002, pg. 20–26, 49)

Many organizations overlook the preparation stage. Companies feel that once they have completed one inspection, they don't need to invest time and resources preparing for the next one. This is probably true in many cases, but it does not negate the fact that companies should make a concerted effort to focus on improvements, no matter how minor they seem. Here is a checklist of items to consider:

- Improve standard operating procedures (SOPs) at the corporate and local levels. Lack of responsibility, improper training, and not following SOPs are frequent organizational problems.
- Scrutinize monitoring programs to ensure they are implemented properly. Ensure that sampling locations are selected based on their criticality; results are reviewed and trended; and appropriate corrective actions are taken when out-of-spec results are found. Document your corrective actions properly, and be prepared to show that the problem has been corrected.
- Establish a validation program with general guidelines, and assign personnel responsible for managing it. Create a validation master plan (VMP) that includes a list of validation activities and a timeline for completion. Ensure

that the VMP is updated as priorities change, and document why a specific deadline was not met and when it will be on the timetable.

- Examine batch records carefully. Improper analysis of data and improperly investigated and closed deviations are frequent sources of citations.
- Review the deviation and corrective actions process and evaluate the change control programs annually.
- Train employees frequently.
- Document everything.

Part 2: Conducting the Audit (October 2002, pg. 30–35)

During final preparation for an audit, companies should review previous inspections and complete any open items. They should also institute an operation plan for use during the inspection to make sure the inspection runs smoothly. We recommend contacting personnel and ensuring that the work environment, documentation, and facilities are in order.

Once the inspectors have arrived, work with them to provide proper documentation and accurate information. Do not panic or become confrontational during the inspection. Respond as quickly and accurately as possible.

determine whether this was simply an isolated incident in the documentation of that specific validation package or a general practice in which all validation packages lack that element.

When developing a response provide a corrective action plan to remedy the observation. Establish why you think the corrective action will resolve the situation, and create a mechanism — such as a new SOP that controls and monitors the steps — to show that this problem has been corrected and will not occur again.

Provide a timetable for the completion of the corrective action plan, and make someone responsible for enforcing it. Be realistic about how long it will take you to solve the problem. Generally, people in a state of panic do not realize what they are

committing to until after they've made the commitment. Making promises you can't keep can lead to noncompliance in the future. So create a realistic timetable; and depending on the issue, establish a long-term program within the timetable. Also, include in the timetable a proper training program, and ensure that department managers agree to meet specific deadlines.

If you disagree with an observation, make sure your response is based on facts and has verifiable data and documentation as supporting evidence. Present your evidence as clearly as possible.

After each observation is studied carefully and appropriate corrective actions with proper deadlines are agreed on, prepare a detailed response document. List each observation with the proper responses

Validation from Past to Future

No one knows for sure what the future holds, but one thing is definitely true: The industry will change dramatically over the next 15 years, and rules and regulations that are in place now will not be relaxed or forgotten.

Two decades ago general inspections focused on processes such as sterilization and general documentation issues. In the early to mid-1980s, issues such as proper cleaning procedures and

cleaning validation emerged. More recently, issues relating to automated systems validation and citations have started to dominate observations. As technology evolves and more systems and operations are automated, the issues that are unique to automated systems validation, use, and maintenance are frequently targeted during inspections. Validation issues related to electronic signatures and data handling are also

receiving a lot of attention. There is no question that automated systems, paperless records, and numerous computerized systems will shape the future of manufacturing operations in the industry. So pay attention to establishing appropriate policies and practices, and training and retaining talented employees with the expertise to adapt to this evolving environment.

separately. Avoid general responses such as "All the above citations will be resolved by . . ." Instead, list each item separately, and assign separate completion dates for each.

Follow-Up

After submitting your response to FDA, several months may pass before the agency replies. Do not wait for FDA to respond before implementing your action plan; start work immediately. If the agency disagrees with the steps you have listed, then adjustments can be made later. Inspectors always consider what steps have been taken in good faith to resolve the issue, and they will be more sympathetic if some corrective action has been started. Begin resolving the problem as soon as possible — don't wait until told to do so.

Assign an internal committee to monitor the progress of each corrective action. This can be the same management team that developed the original response, but make sure they have the authority to monitor the progress.

The committee is also responsible for determining the priority of each observation and assigning individual managers or functions to implement each item and report back. Status reports should be given weekly or monthly based on the severity of the issues.

To assist in reporting, design an internal system to track the status of each observation and monitor actual completion dates. Compare the completion dates to the commitment dates. Most large companies use corrective and preventive action (CAPA) systems for this purpose, but a spreadsheet also works. When using the

CAPA system or developing the spreadsheet, consider the number of observations, the size of the company, and the number of people involved in resolving each issue. If the data are stored electronically, back up your observation monitoring system regularly. Eventually, the system should provide real-time status reports.

Lessons learned. Finally, develop a "lessons learned" document. This document will provide an overview of the entire inspection, explain the thought processes behind the decisions made, and identify strengths and weaknesses. Talk to individuals involved in the inspection, and get their feedback on areas of improvement. Publish this "lessons learned" document internally, and ask employees, "What would you do differently if you had to go through the inspection all over again?" Chances are they will have to apply their responses in the next inspection.

Turning Lemons into Lemonade

When faced with a difficult issue or problem, turn it into something positive. Biopharmaceutical companies need to look beyond enforced compliance and be aware of the residual benefits of an audit, like these.

- Employee productivity improves as a result of better and more frequent training initiatives.
- The implementation of new computer systems and manufacturing equipment can reduce overhead costs.
- Documentation and process improvements can lead to more efficient operations.
- Breakthrough ideas can change industry standards and lead to new scientific and technological advancements.

Suggested Reading

Agalloco, J.P., *Validation of Pharmaceutical Processes: Sterile Products Revised*, 2nd ed., F.J. Carleton, Ed. (Marcel Dekker, 2000).

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