Assuring the Effective Use of Standard Operating Procedures (SOPs) In Today's Workforce

SOPs are critical to efficient operations, quality control, and regulatory compliance.

Sep 2, 2006
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Every year, the US Food and Drug Administration issues scores of Warning Letters to pharmaceutical, medical device, and biologics companies. Although Warning Letters can be triggered by situations such as customer complaints and whistleblower statements, the majority follow an inadequate company response to a Form 483 issued by FDA after an on-site inspection has identified potential violations of regulatory requirements.

Surprisingly, many companies' violations center on failure to have, or to properly use, Standard Operating Procedures (SOPs), the most fundamental component of current Good Manufacturing Practices (cGMPs). Although different regulations apply to each of the life sciences sectors, SOP compliance is required for all companies within those business arenas.

SOPs and Quality

The purpose of an SOP is straightforward: to ensure that essential job tasks are performed correctly, consistently, and in conformance with internally approved procedures. Clearly, employees' correct, consistent performance of essential job tasks is as much a business and quality issue as it is a regulatory requirement.

Quick Recap

By its nature, poor employee performance has a negative impact on overall operational performance. That impact may be even greater than recognized by many organizations, with some studies suggesting that up to 40% of operational inefficiencies can be attributed to employees' failure to fulfill their job responsibilities. Even companies that have implemented costly process improvement systems continue to feel the operational impacts of "human error" on their efficiencies and quality control.

Few industries are more vulnerable to risk than the life sciences sector. Although all industries share a financial vulnerability resulting from operational inefficiency, the liability associated with compromised product quality can hit a life sciences company particularly hard. Compromised product quality can easily result in product recalls, regulatory enforcement, and governmental litigation, but even the suspicion of quality problems can send patient, healthcare professional, and stakeholder confidence plunging. With highly publicized product recalls still fresh in the minds of the public and regulators, life sciences companies and their products are coming under greater scrutiny than ever before. And, because FDA's Warning Letters are public information, public scrutiny is quickly fueled by news reports via the media or the Internet.

Although FDA has long emphasized the importance of SOP compliance, the Agency's evolving focus on quality as the driver of compliance adds weight to the importance of a comprehensive corporate approach to development and use of SOPs. Warning Letters routinely conclude with a sober reminder

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that "... violations may result in FDA taking regulatory action without further notice to you." FDA has an arsenal of actions it can impose, from confiscating product inventory to initiating product recalls, assessing civil penalties and fines, or pursuing criminal prosecution.

SOP Compliance

FDA's definition of an SOP is deceptively simple. SOPs are, according to a variety of FDA regulations, written procedures that accurately describe and detail essential job tasks. For example, in 21 *CFR* 211.100, the regulation states: "There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit."

Beyond the written procedure, SOP compliance includes a requirement to train employees on essential job tasks, something expressed in 21 *CFR* 211.25, which applies directly to the pharmaceutical industry, but is applicable to all life sciences industries. "Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, experience, or any combination thereof to enable that person to perform the assigned function." It is this combination of written procedure and employee training that assures the quality of a drug product or medical device being tested or manufactured and its compliance with applicable FDA regulations.

Understanding the purpose of SOPs is one thing; complying with the FDA's regulatory standard for ensuring that employees have the knowledge they need to perform their job functions is something else entirely. Large companies may have thousands of job tasks, each one requiring an SOP that usually needs regular updating. Even small companies will have extensive SOP requirements, whether it's for regular equipment calibration or for sterile manufacturing procedures. In fact, FDA has specifically identified operational areas that fall under cGMP and—by extension—SOP regulation. The components for which employees must have sufficient knowledge to perform their job functions adequately, range from buildings and facilities to equipment, components, and drug product containers and closures, production and processes, packaging and labeling, holding and distribution, laboratories, and returned or salvaged drug products.

In general, SOP compliance incorporates activities that can be grouped into five categories:

1. Creation of a quality control unit responsible for ensuring SOP compliance

2. SOPs for each job task that are updated and understandable to employees

3. Accurate, timely distribution of SOPs to all responsible parties, validation that the SOP has been received and read

4. Confirmed employee comprehension of the SOPs and the ability to apply the knowledge contained in the SOP

5. Comprehensive corrective and preventive action program to identify rectify and prevent quality failures.

The Quality Control Unit

FDA signaled a new approach to cGMP compliance by pharmaceutical and biotechnology companies in September 2004. The Agency's "...modern quality systems and risk management approach" to cGMP emphasized management responsibilities for quality control and assurance. That responsibility included formation of a quality control unit that "... shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products." Although the compliance responsibility of the quality control unit is not limited to SOPs, an effective SOP compliance program is central to the unit's ability to fulfill its mandate.

Although life sciences companies routinely embrace the most advanced technologies in the laboratory and manufacturing plant, many companies have not been as receptive to technology managing their SOP activities. Given the scope of modern SOP compliance responsibilities and the consequences of noncompliance, companies increasingly recognize the value of using technology to comply with SOP mandates. Not coincidentally, the same system that supports SOP compliance can also easily serve as the foundation for improving a company's overall quality control management and assurance effort.

An effective SOP compliance program requires a technology-enabled platform that is interoperable with existing technologies and performs multiple functions, including SOP distribution, validation, testing, and recordkeeping in audit-ready formats. Because SOPs require revision with every process change, equipment replacement, or regulatory change, any SOP management technology should

enable rapid updating and distribution. Just as important, the system should allow effective targeting of SOPs to the correct employees, thereby preventing all employees from being overwhelmed by SOPs not applicable to the individual's job tasks.

The Written Word

The FDA requires that SOPs be in a written format. Violation of that basic requirement is routinely found in FDA's Form 483 or in Warning Letters for a variety of operations throughout the regulated process. Significant deviations noted by FDA in recent Warning Letters illustrate the range of activities that may be targeted for failure to meet the written SOP standard. For example:

1. Failure to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile

2. Failure to establish written procedures applicable to the function of the quality control unit

3. Failure to establish written procedures for evaluating quality standards of each drug product to determine the need for changes in drug product specifications of manufacturing and control procedures

4. Failure to develop written procedures for surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences

Although SOPs vary from company to company—and sometimes from facility to facility within the same company—they should all have a consistent format that reflects applicable regulatory compliance requirements and includes "how-to" information specific to the job task (Figure 1).

Figure 1. An example of a standard operating procedure

Because the purpose of an SOP is to ensure consistent, compliant performance of employees and processes, it goes without saying that SOPs should be understandable to users. Unfortunately, many SOPs are not. The FDA requires that authors of SOPs be qualified individuals with necessary technical and compliance experience and expertise in the particular subject matter addressed by the SOP. Yet, those qualified authors, despite their experience and expertise, may lack the necessary writing, instructional design, and technical skills to effectively communicate with workers with different learning needs. In addition to varying literacy levels, companies increasingly face the challenge of presenting SOP information in multiple languages, or in conformance with different cultural norms. That challenge is unlikely to shrink. Even as life sciences companies continue their global expansion, they are likely to be held to the same SOP requirements, either imposed by FDA or by comparable regulatory authorities in other countries.

Fortunately, technology now offers alternatives to the infamous SOP manual that afflicted generations of employees with incomprehensible material. Internet-based technologies can produce SOPs that cut through the fog created by pages of written explanations. Graphics, animation, sound, and simulation can be employed to illustrate proper procedures and processes, rather than merely explain them. Skillful use of these instructional techniques can engage employees and enhance comprehension, ensuring that the SOP's intent is achieved. Optimally, SOPs are developed by teams of professionals, equally proficient in the subject matter as in technology, the learning psychology of adults, and interpersonal communications.

Distributing SOPs

SOP distribution may appear simple and easy. It is neither. Hundreds or thousands of SOPs that change regularly with any shift in regulation, corporate policy, or production process can easily affect hundreds or thousands of employees. It is not unusual for employees to experience, within a relatively short period of time, SOP versions one, two, and three for the same job task.

The FDA requires that SOPs be distributed in a timely manner and that each employee validate the receipt and understanding of it. The volume of material that must be distributed, validated, and stored virtually requires a technology-enabled system, such as an Electronic Data Management System (EDMS). Dozens of vendors offer SOP or document management systems, but not all systems are equal. An optimal system must comply with all Part 11 regulatory requirements, provide secure access for program monitoring and management, and store data in an audit-ready format that is quickly available for FDA examination during an inspection or investigation.

Ensuring Comprehension

The days of simply distributing information to fulfill regulatory requirements are long gone. Today, the standard of SOP compliance requires that SOPs be applied. "Failure to follow written procedures" occurs frequently in FDA's 483s and Warning Letters, suggesting that employees neither understood nor applied the necessary knowledge to properly fulfill their job responsibilities. Interestingly, many of these violations occur in companies compliant with basic SOP requirements related to written

procedures, and distribution and validation of employee receipt and understanding of the SOP. Yet, those same companies often lack a mechanism to confirm comprehension.

All SOP programs should incorporate testing or evaluation features that clearly establish an employee's level of comprehension for any individual SOP. Online-based testing gives managers immediate access to this information, promoting timely responses to identified knowledge gaps. Just as important, testing documentation assures regulators of a company's commitment to effective employee education rather than simple document distribution.

Responding to Inadequacies

The obvious intent of an FDA Form 483 or Warning Letter is to promote prompt, voluntary corrective action to inadequacies uncovered during FDA inspections. The 483 gives inspected facility owners the first opportunity to correct compliance violations and implement procedures to prevent them from occurring in the future. Warning Letters are issued for significant regulatory violations that warrant enforcement action if they were not corrected. Often, an inadequate corporate response to a 483 is followed by a Warning Letter that concludes, "Please advise the Agency regarding your corrective action plan to address the problems described above..." and sets a firm deadline for a written response.

A Warning Letter opens the door for a company to work with FDA in achieving compliance. Responding to the Letter effectively is the first step, and it is a critical one, to minimize the likelihood of an FDA enforcement action. Several factors should be considered in developing a response to an SOP-related Warning Letter, including:

1. Warning Letters can indicate isolated violations or systemic problems throughout an enterprise. Inadequate SOP training observed by FDA in one job function at one facility may indicate a much broader problem. Understanding the potential scope of the problem, rather than simply focusing on a specific violation noted in the Warning Letter, will enable the company to respond to all violations and improve its own compliance performance. If you disagree with the facts or analysis by FDA, or if you believe no additional actions are necessary for an identified violation, explain your position clearly to FDA. Remember, however, that FDA has the final word. In a 2004 Warning Letter, for example, FDA responded to the company's assertion that "The need and adequacy of training is routinely assessed as part of the internal audit program. We have no evidence that there are systemic training issues." FDA writes, "The production mistakes of two reportedly trained employees, the failure of a supervisor to properly document employee training, and the failure of your internal audit process to identify these weaknesses, suggest that there are problems requiring your attention."

2. Prepare a response to the Warning Letter. The response should include specific actions for any identified violation, from developing new SOPs to monitoring by the quality control unit. Be careful not to promise more than you can deliver. FDA takes corrective and preventive action plan implementation very seriously. If you have questions about violations, contact the FDA District Office for additional information, or request a meeting with FDA. Submit a response within the identified timeframe, typically 15 days.

3. Of utmost importance to FDA is that a company demonstrates an acknowledgement of the seriousness of the observed violations, a reasonable sense of urgency (with specified target dates), and that corrective actions clearly prove (with data or evidence where possible) that the compliance issue has been resolved.

Compliance and Performance

Standard operating procedures, whether developed to meet regulatory compliance or to reinforce corporate policies, are critical to efficient operations, quality control, and regulatory compliance. When properly designed, distributed, and tested, they provide employees with practical, understandable information that enable safe and efficient job performance. When properly managed and monitored, SOPs equip employers with a clear view of existing knowledge gaps and potential inefficiencies caused by inadequate training. And, for any company on the receiving end of a 483 or Warning Letter, they represent an opportunity to achieve compliance and improve operational efficiency —simultaneously.

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