Pharmaceutical Technology®

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Biopharma/Pharma Analysis: Don't Leave Change Control to Chance

- Top 10 Change Control Challenges
- Avoiding Murphy's Law
- Change Control for QA and Risk Management
- Maintaining GMPs with Vigilance
- Change Control for SOPs

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Top 10 Change Control Challenges in the Pharmaceutical Industry

Meeting the challenges of change control management requires strategic change control planning and processes, robust quality systems and partnerships with cGMP-compliant raw material suppliers that have strong global supply chain and international regulatory expertise.

1 Applying Quality Risk Management (QRM) Principles To Change Control

Quality risk management (QRM) is a comprehensive and continuing process that provides a framework for understanding and mitigating risk through robust controls. Pertinent worldwide, QRM aims to minimize risk to product quality through evaluation, control, reporting and review of risk. In the development and manufacturing of pharmaceuticals, biopharmaceuticals and other therapeutics the U.S. Food and Drug Administration (FDA) holds the drug manufacturer's Quality Control unit responsible for proper assessment of any manufacturing change and the impact the change may have on the drug product. Utilizing QRM in change management/

change control, documentation and quality defects can result in more efficiency and effectiveness, but the challenge is in formally applying and implementing QRM to change control, deviations and other quality systems.

2 Ensuring a Proactive Change Management System

Change control is a consequential component in meeting regulatory, compliance and quality requirements. Establishing a change management system that stays current in meeting all requirements and mitigating risk mandates the following:

- In-depth knowledge of regulatory and compliance obligations
- Industry best practices for quality control and change management
- Planning for possible changes and delays
- Documentation and validation

The challenge for many pharmaceutical manufacturers is that their change management system in place has been a "reactive" one for years. Best practice is a change management system that is constantly proactive, not merely reactive. Change control management is a complicated task that can be assisted by cGMP-compliant suppliers with a global supply chain network and experience with international regulatory and compliance demands.

3 Following Change Control Procedures Organization-Wide

The FDA considers change control programs essential elements of pharmaceutical quality assurance systems. Change control is the responsibility of the whole organization. Previously, manufacturers relied on separate departments for their own change control, often resulting in inconsistencies in communication, collaboration and documentation causing costly mistakes and risks.

Change control programs, including quality assurance and quality control, are the duty of every employee. Management's challenge is to clearly communicate this organization-wide. Some solutions include:

- Making certain every employee knows required procedures and regulations that must be followed and regulatory and compliance consequences for failure to do so
- Scheduling of regular compliance communications to employees
- Establishing a system for quickly communicating to all employees (across multiple locations, different shifts, etc.) about quality issues
- Maintaining open channel for employees to quickly notify management of an identified problem or potential issue

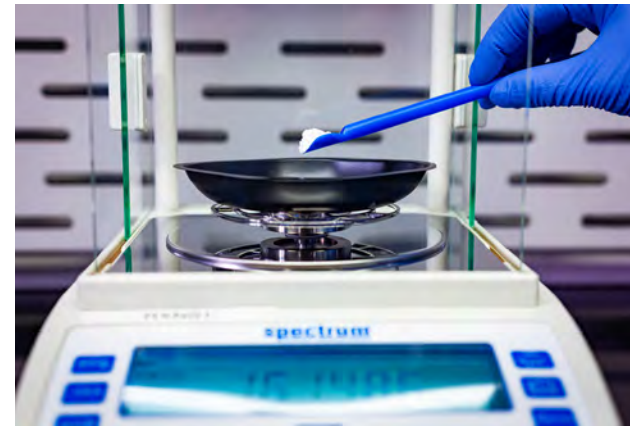
4 Mitigating Supply Chain Disruptions

The complex global supply chain is still recovering post-pandemic and is also susceptible to disruption by weather, geopolitical and other external events. A robust change control system must incorporate plans for dealing with supply chain interruptions. High-purity raw materials are critical to the exacting quality standards required for biologics, vaccines and other pharmaceuticals through all stages of discovery and development. Raw material changes can be pivotal and disruptive, necessitating changes to suppliers, component specifications and much more.

The change control system must accommodate the tracking and reviewing of raw material changes as well as provide the appropriate documentation for change justifications. In addition, change control must include raw material suppliers that can be relied on to strictly follow change control procedures before there is any processing of components impacted by changes.

WHITE PAPER

Accelerating the Bench to Bedside Timeline



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5 Documenting SOPs for Compliance

Standard Operating Procedure (SOP) defines the requirements to ensure changes to systems, products, processes, procedures and documents that impact product quality and compliance are evaluated, documented and approved prior to implementation and closure.

There must be an SOP detailing the change control program and that has been approved by the Quality Unit. The SOP needs to ensure all GMP changes are reviewed and approved. SOP testing and verification help produce consistent results for every pharmaceutical manufacturing process, batch or lot. Writing and implementing SOPs can be particularly challenging. Poorly written SOPs are a common cause of deficiencies and observations cited in 483s and FDA warning letters. From October 2021 through September 2022, the FDA issued 80 citations for poorly followed or documented procedures and gave out 44 citations for the absence of written procedures.

6 Assessing Change Impact Prior to Implementation

Lack of effective change management can cause many problems and result in setbacks, costly delays and increased regulatory scrutiny. Following change management procedures often requires assessing risk and especially determining the potential impact of changes that become necessary to implement. Where drug products are concerned, change control is expected to correct or significantly reduce product quality risks and/or patient safety hazards to acceptable levels, without increasing additional risk.

A change impact assessment examines the consequences of making the change and should identify:

- All files, documents and SOPs that may have to be modified if the change is made
- Employee training required for new procedures or processes caused by the change
- cGMP practices that may be impacted
- New costs, tasks and time needed to implement the change

An effective change control system ensures that any changes introduced help the pharmaceutical manufacturer's processes, products, facilities, equipment and systems remain compliant and validated.

7 Viewing Change Control as a GMP-Compliance Issue

Change control is viewed by the FDA as a critically important GMP compliance issue. It is one of the main criteria the FDA uses in determining its drug inspection coverage, and the agency's decision for follow-up regulatory actions such as issuing Warning Letters.

Some of the major GMP deficiencies related to change control issues that have been flagged by the FDA include:

- Failure to file changes with the FDA
- Inadequate review and approval
- Changes by the Quality Control unit
- Failure to evaluate FDA filing requirements, for example, failure to file for a prior approval or changes being enacted

The FDA expects the Quality Control unit to be integrally involved in the change control process, and the agency usually holds Quality Control responsible for change control deficiencies.

8 Providing Management Oversight of Change Control System

It may be true that pharmaceutical change control is challenging, time-consuming and requires a "whole lot of red tape" because of quality assurance, compliance and regulatory agencies. However, well-functioning change control executed thoroughly can protect product quality, patient safety and the manufacturer from liability, reputation damage, loss of revenue and potential lawsuits.

To meet the challenges and legal demands, the responsibilities of company leadership regarding change control include:

- Providing high-level analysis of business processes and systems to identify and correct any deficiencies and safeguard assets
- Planning specific change through the change control system including risk assessment to monitor and mitigate key risks
- Maintaining transparency and ensuring compliance with policies, regulations and ethical standards
- Achieving continuous improvement through due diligence, best practices and adopting new technologies

9 Monitoring Post-Implementation

After implementation of a change an evaluation of the change needs to be undertaken to confirm the change objectives were achieved and that there were no unintended consequences. Procedures must be followed for confirmation and validation that the change took place and had no negative impact. Lack of complete change control documentation such as full post-implementation reporting is a common regulatory failure.

Best practices include monitoring the change after implementation to ensure maintenance of the change objectives and to detect any residual risks. These activities may take the form of increased quality checks, a higher level of testing, or more in-house inspections. Post-implementation quality activities should be included in the change control plan and records maintained of the activities.

10 Staying Vigilant to Ensure Changes Go Through the Change Control Process

Establishing a robust and effective change control system is critical for pharmaceutical manufacturers to stay compliant. Senior management must operate with strong vigilance to ensure that change control is consistent and comprehensive.

In GMP inspections the FDA frequently finds inefficient or inadequate change control procedures including:

- Changes implemented without change control procedures followed
- Failure to assess change impact prior to implementation
- Change implemented before employees are informed and trained
- SOPs not evaluated or revised considering the change
- Change proposal lacking adequate justification
- Documentation for a change control does not include the actions that need to be performed in conjunction with the change
- Failure to incorporate effectiveness checks to determine if the change is working and meeting the specified criteria
- Change proposal does not contain evaluation of how changes may impact the drug application ■

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From Wrong to Write

Avoid Murphy's Law with Robust Quality Assurance and Change Control

By Matt Szap, Ph.D.

An effective change control system should ensure better quality by focusing on continual improvement to reduce risk.

In the highly regulated pharmaceutical industry, adverse events can precipitate a cascading effect of negative consequences worldwide. To comply, pharmaceutical manufacturers are required to maintain **robust** quality assurance and quality control systems, implement **robust** change management and change controls, and distribute drug products through a **robust** supply chain — all while ensuring their processes are thoroughly documented.

While many pharmaceutical manufacturers strive to institute robust processes, are they *really* meeting the true definition of the word "robust"? In other words, are they "strong, healthy, vigorous, powerful?"

- How strong and healthy are your change control processes and procedures?
- How powerful is your quality assurance and quality control?
- How vigorous is your supply chain management?

Only by implementing a truly robust quality assurance program backed by extensive documentation can pharmaceutical manufacturers avoid Murphy's Law and go from wrong to "write".

Anything that can, could have, or will go wrong, is going wrong, all at once.

–Murphy's Quantum Law

WHEN IT ISN'T ROBUST

The heparin adulteration in 2008 is an example of the havoc and harm substandard materials entering the global supply chain without transparency can cause to patient health and safety, as well as public confidence in medications, increased regulatory scrutiny, and ongoing international lawsuits.[1]

A contract laboratory sourced what it thought was adequate-quality porcine heparin from China. The heparin was contaminated with oversulfated chondroitin. The contamination was not discovered until after it had been used in a formulated drug product administered to patients. The adulterated heparin killed 81 people in the U.S. and left another 785 severely injured.[2]

At least 11 drug products and 72 medical devices containing heparin were recalled by 15 U.S. companies. Heparin products were also recalled in Australia, Denmark, France, Germany, Italy, Japan, Sweden, and Switzerland.[3] The FDA was unable to pinpoint the exact source, or sources of the heparin adulteration, but evidence suggests it was likely introduced by entities upstream of the Chinese API production site, Scientific Protein Laboratories–Changzhou (SPL-CZ).[4] Pew reported the heparin incident revealed supply chain management and oversight failures including insufficient quality control systems for incoming raw materials.[5]

The heparin incident illustrates the necessity of following strict controls for compliance and quality, as well as reinforces how critical it is for pharmaceutical manufacturing management to partner with experienced, responsible current Good Manufacturing Practice (GMP) raw materials suppliers with a reliable global supply chain network.

In February 2023, two eye drop products, sold under the names EzriCare® Artificial Tears Lubricant Eye Drops and Delsam Pharma Artificial Tears Lubricant Eye Drops, were recalled by their manufacturer, Global Pharma Healthcare, due to potential bacterial contamination. The recall was expanded to include Delsam Pharma Artificial Eye Ointment as well. As of this writing, there has been one mortality and eight reports of vision loss so far, with more cases developing.[6]

In a statement, the FDA said it had recommended a recall of the medicine due to the company's current GMP violations, including lack of appropriate microbial

testing, formulation issues, and lack of proper controls concerning tamper-evident packaging.[7]

As of March 1, 2023, the CDC, in partnership with state and local health departments, identified 64 patients in 13 states with VIM-GES-CRPA, a rare strain of extensively drug-resistant *P. aeruginosa*. The bacteria can cause severe disease, blindness, and death.[8]

These adverse events and risk of mortality shine a spotlight on the crucial importance of raw material quality in drug development and commercialization, as drug products must be consistently safe and reliable for patients worldwide.

Global consulting firm McKinsey & Company has stated, "Prevention of major compliance issues can, in itself, be worth millions in cost savings."[9] Over the years, global drug product recalls have cost pharmaceutical companies millions in lost revenue, fines, and protracted lawsuits with patients ultimately paying the heaviest price.

RESOURCE

Navigating High Purity Waters

LACK OF QUALITY ROBUSTNESS

According to the FDA, many pharmaceutical manufacturing failures can be traced to failures within a company's quality system. In some cases, the quality system ignored or failed to respond to customer complaints. In other cases, multiple repeated deviations were treated as separate incidents, rather than an obvious trend.

The FDA also highlights that another reoccurring matter has been investigations that conclude with no additional understanding or insight into why the problem may have occurred. Thus, there is no pathway established for prevention. Without the root cause of the problem identified, there is failure in assuring continual improvement of the process.

Quality management needs to extend across the product life cycle and throughout the supply chain. Quality assurance is proactive, not reactive. It consists of incorporating proactive measures early in development and actively managing them with the goal of continuous improvement to ensure quality outcomes.

Courtesy of Spectrum Chemical Mfg. Corp.

ROBUST CHANGE CONTROL

The FDA looks to pharmaceutical manufacturers to have robust change control as part of the quality assurance program. This includes a formal change control plan that identifies actions, inputs, outputs, and control limits, and defines successful achievement of the desired change. In addition, it should also contain:

- a record of successful completion and review of the plan's required elements and supporting data
- regulatory approvals obtained for the changed state before the product made under the change is released to market
- implementation of any new or updated GMP documentation
- appropriate staff training

Robust change control is critical to successful compliance. Inadequate change control is one of the top 10 FDA 483 and Warning Letter citations. The FDA reviews change control documentation to determine that changes have not impacted products, processes, or equipment negatively. Lack of thorough change control can lead to adverse events as well as require costly remediation.[10]

All changes must be risk assessed, validated, implemented, and completely documented. Major changes may require regulatory filings and/or prior regulatory approval.

CONCLUSION

An effective change control system should ensure better quality by focusing on continual improvement to reduce risk.

Murphy may not have known about change control. However, in considering what can go wrong, how strong, healthy, powerful, and vigorous is your **robust** change control process?

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Change Control: Blueprint for Quality Assurance and Risk Management

Q&A with Spectrum Chemical President & CEO Russell Kneipp

Russell Kneipp
Spectrum Chemical
President & CEO

Change control plays an important role in pharmaceutical development and production. It ensures a change does not negatively impact a drug product's safety, quality or regulatory compliance. As new compliance requirements govern change management processes, Russell Kneipp, President and CEO of Spectrum Chemical Mfg. Corp., offers his perspective on how suppliers like Spectrum Chemical are responding to the need for more robust global quality systems and change management processes – and what the future may hold.

PharmTech: Why is change control a focus area for Spectrum Chemical and its customers?

Kneipp: Change control management is about quality and extends throughout a pharmaceutical manufacturer's labs, production facilities, packaging, employee training and more. As a raw material supplier, we know that any changes in the materials we provide can impact our customers. We take that very seriously, so we offer change guidance, support and notifications in those situations that involve a change in raw material whether it's proactive or reactive. Proactive change control involves a change planned in advance. Reactive change control occurs when an unplanned change happens and must be mitigated to avoid any negative consequences. This was the case during the COVID-19 pandemic, for example.

PharmTech: What is Spectrum Chemical's approach to change control?

Kneipp: We've been working within regulated markets for more than 50 years, so we have put a lot of structure, systems and processes in place to serve our customers. This includes proactively communicating to our customers any significant changes, deviations or departures in manufacturing or sources that can alter or impact the quality of a product. When we talk about change control, we basically rely on two major definitions. One is full change control, in which we notify our customers of any changes that can affect product quality. This can involve changes in raw material source, composition, formulation, manufacturing process, packaging, specifications or even a change in supplier. The other involves a manufacturer lock, which means we "lock" the customer's raw material supply to a single-source supplier. If the raw material manufacturer needs to change for any reason, we notify the customer ahead of time for approval.

PharmTech: How does your approach to change control benefit your customers?

Kneipp: Our goal is to fulfill customers' expectations on a timely basis, helping them manage change, mitigate risk and meet industry standards of quality and safety. Whenever we onboard a new customer, we work with them to assess their change control requirements. We are cGMP-compliant and we know our customers understandably have very high quality expectations. We scrutinize our own suppliers, and we do extensive testing of raw materials in our own in-house analytical labs. We document all that information and provide scientific dossiers to our customers to help them meet their own global regulatory and compliance requirements. We know these are critical to successful discovery and development of new drugs and biologics.

PharmTech: What are some pitfalls if change control procedures are not robust throughout the supply chain?

Kneipp: Best practices in supply chain strategy aim to reduce risk through control at every step of the supply process from planning and sourcing to production and product delivery. In other words, it's about supporting quality initiatives that ensure drug products are of the highest quality.

Without proper and complete documentation, especially quality and change control, it is extremely difficult for pharmaceutical manufacturers, suppliers and distributors to be able to trace problems back to their source. This lack of transparency can result in serious negative consequences if quality and change control procedures and processes are not scrupulously executed.

If not addressed, there is a real danger of drug products of poor quality being manufactured. Such scenarios have occurred resulting in patient injuries and deaths, global product recalls and international lawsuits. Lack of transparency can also contribute to imitation drugs fraudulently entering the global supply chain.

Best practices in supply chain strategy aim to reduce risk through control at every step of the supply process from planning and sourcing to production and product delivery.

Courtesy of Spectrum Chemical Mfg. Corp.

Failure to meet compliance and regulatory requirements is another pitfall. The pharmaceutical supply chain must meet compliance, good distribution practice and numerous other regulations. Pharmaceutical manufacturers need to ensure their internal quality and compliance systems including change control are efficient to successfully produce drug products that are compliant and safe.

In order to help them maintain the highest cGMP standards, manufacturers should partner with cGMP-compliant suppliers with a track record of global supply chain experience, reliability and responsibility.

PharmTech: When screening potential suppliers, what should pharma manufacturers look for to ensure they have proper change control procedures?

Kneipp: Manufacturers expect suppliers to have an established change control system

for reporting applicable changes to their customers. These supplier-initiated change notifications (SIC) report any changes to raw materials, manufacturing methods, product testing and production equipment. Change control procedures and change management can also be covered in a quality agreement between the customer and supplier. In the pharmaceutical customer-supplier relationships, effective change management comes about through effective communication and collaboration. Both organizations should be actively involved in change management actions, particularly those activities that may directly impact product quality. By sharing change management activities, risk can be further mitigated and negative impact avoided.

PharmTech: What trends are you seeing in the market that might further elevate the importance of change control?

Kneipp: There are two trends dominating: digital transformation and supply chain transformation. New technologies like advanced data management, analytics and automation will contribute to streamlining quality and change control processes and procedures leading to more robust risk management. Digital innovation will provide centralization of data to pharmaceutical manufacturers that will make it more efficient, easier and faster to identify and assess risk as well as justify and validate change. Communication and collaboration with manufacturer and raw materials suppliers will be accelerated.

Another improvement digitalization may provide is greater visibility and transparency in both quality and change control. While still only in its earliest stages in supply chain management, the adoption of innovative technologies and digitalization will also transform the global supply chain, addressing inefficiencies and increasing agility and resiliency.

PharmTech: What implications do you see in the ongoing "globalization" of pharmaceutical and biopharmaceutical manufacturing?

Kneipp: Quality control and change control adherence will continue to play a significant role as the global supply chain is heavily regulated and complicated by compliance and quality variations around the world in both mature and emerging markets. These unsuitable variations are particularly consequential for multinational pharmaceutical companies who have manufacturing facilities in many countries.

To mitigate these variations and other risks, pharmaceutical manufacturers can seek partnership with a global supplier like Spectrum Chemical that can provide technical support and guidance, regulatory compliance standards, supply chain transparency and a global distribution network. With our knowledge of international quality standards and decades of global supply chain experience, we can provide global supplier network advantages to multinational pharmaceutical manufacturers. ■

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Maintaining GMPs Requires Continued Vigilance

By Susan Haigney

Maintaining good quality control practices throughout the entire manufacturing process requires robust development, a drive toward product and process understanding, and pre-established, comprehensive written procedures that are consistently reviewed and updated.

Good manufacturing practices (GMPs) are established by regulators to ensure that pharmaceuticals are safe and effective for the patients that rely on them. In the United States, requirements governing finished pharmaceutical quality are described in the Current Good Manufacturing Practices (cGMPs) regulations established by FDA and published in the *Code of Federal Regulations* (Title 21 of the *CFR*, parts 210–211 for most finished pharmaceuticals). FDA also publishes guidance to further describe recommended practices for complying with the cGMP regulations. The agency states that "cGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities. Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that

manufacturers of medications adequately control manufacturing operations."[1]
In Europe, GMPs are defined by the European Commission in *EudraLex*–Volume 4–Good Manufacturing Practice (GMP) guidelines[2], which were first published in 1989. EudraLex states that quality management is "a system of marketing authorizations [that] ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality, and efficacy."[2]

RESOURCE

Scientific Documentation

To harmonize GMPs and other quality requirements worldwide, the International Council for Harmonization (ICH) works with international regulators and industry to develop common guidelines across the industry to ensure consistent quality expectations worldwide.

"At its core, cGMP is a science- and risk-based focus on assuring drug quality. As described in ICH Q10, *Pharmaceutical Quality System*, an overall attitude to drive meaningful and continuous improvements from the quality unit and other manufacturing employees is essential"[3], FDA told *Pharmaceutical Technology*.

The global nature of the pharmaceutical supply chain requires regulatory agencies to inspect and govern GMPs at manufacturing facilities. These inspections sometimes result in actions by regulators (e.g., FDA 483s, warning letters, import bans, and court actions) against companies that fail to follow GMPs. Common cGMP deficiencies cited by FDA in warning letters sent to pharmaceutical companies inspected during the past year include failures to ensure product sterility, ensure data integrity, create quality control units, and develop and follow written procedures.[4-7]

"Companies should vigilantly encourage manufacturing practices that reflect the most current and robust methods of processing and control, and with a focus on providing a quality product to US consumers," says FDA. "The approach to successful cGMP is not merely a check-box approach where a single obstacle can be identified, nor is it meant to be unchanged throughout the life of a product or a facility. Using a holistic and quality risk management approach, a manufacturer can select and study specific products and processes with the goal of continual improvement of product quality and quality systems and widespread optimization."

So how do companies ensure they are "vigilantly" following GMPs and avoid the wrath of regulators? The answer appears to be found in a company's "quality culture" and in the development, writing, and following of written procedures.

ESTABLISHING A QUALITY CULTURE

Performing pharmaceutical manufacturing according to GMPs involves a dedication to quality throughout development and manufacturing processes. "Corporate management plays a vital role in this endeavor by establishing a commitment to quality, which includes providing sufficient resources and oversight for manufacturing operations. There are many elements to successful implementation of cGMPs but measuring and monitoring quality indicators and managing change are key among them," says FDA.

According to Susan Schniepp, executive vice-president of Post-approval Pharmaceuticals and distinguished fellow at Regulatory Compliance Associates, maintaining GMPs throughout all processes and procedures involves a combination of personnel training, keeping tools and equipment updated, having a strong quality unit, and developing a quality culture at all levels of the company. "How the company goes about achieving this objective is what is critical. Traditional training may not be enough. There should be constant on-the-job training and oversight on a continual basis. Upgrading tools and equipment, especially computer-driven programs, needs to involve IT departments and adhere to the current data integrity concepts," says Schniepp. "No one element will be able to sustain GMPs. All the elements work together to establish a culture where sustaining GMPs is a priority."

Chris Moreton of FinnBrit Consulting agrees. "Too often, in my experience, certain factions in an organization think that quality is someone else's responsibility. There may be an organizational chart that shows where the quality unit sits in an organization, but 'quality' (including GMP) is everyone's responsibility within an organization; from the most senior to the most junior and vice versa." Management is key in creating a quality culture, says Moreton. "If the staff see the managers taking an interest and checking on things on a daily basis, the staff will respond, and they will try harder to get things right."

> ***"Too often, in my experience, certain factions in an organization think that quality is someone else's responsibility."***

A commitment to staying current with regulatory expectations is a must, according to Schniepp, and she warns that complacency is the biggest obstacle to maintaining GMPs. "Once a process or procedure is established and functional, there does not seem to be the impetus to update and revise it as regulatory interpretation and understanding changes. This leaves the process or procedure compliant to outdated standards," Schnieep says.

Companies must also learn from prior mistakes, according to Mark Lynch, vice-president of Strategic Compliance at Parexel. "It's best to take the lessons learned from product experience and apply them to the

culture overall so those lessons only need to be learned once. Those experiences should be continuously applied on the product level, and also used to make improvements to standard operating procedures (SOPs), policies, personnel, and technology."

"Companies must also pay continuous attention to problem identification, solution, and improvement. Refinement of problem-solving techniques contributes to organizational learning."

Problem solving is another technique that must be honed, according to Lynch. "Companies must also pay continuous attention to problem identification, solution, and improvement. Refinement of problem-solving techniques contributes to organizational learning."

Enforcing quality procedures through a policy that ties failure to follow procedures with grounds for dismissal and using internal audits to detect improper performance are options to ensuring a quality culture, according to Lynch. "It is also important that tools are a regular topic of discussion with operators to capture improvements and assure consistency. Additionally, sufficient supervisory presence and oversight are key both for monitoring purposes, and to be sure operators can raise questions and get the support they need. Finally, it's best practice to put a reporting mechanism in place that does not require identification, so employees feel comfortable flagging an issue without fear of blame," he says.

LACK OF CONSISTENT GMPs MAY LEAD TO REPEAT OFFENSES

Companies who do not consistently maintain GMPs may find themselves under additional scrutiny by regulators for repeat offenses. A variety of FDA warning letters have pointed out repeat cGMP violations at companies and/or a particular facility.[8,9]

FDA reports that the agency, "... strives to provide clear guidance to companies proactively and in its enforcement actions. Where repeated violations have been found at the same facility or among different facilities of the same firm, we highlight those violations so that they may be addressed adequately. A focus on a commitment to quality is essential to correcting repeated violations, as are adequate corrective actions and procedures. While we generally encourage a focus on overall quality, there are times when we encourage firms to take specific actions, which are included in our warning letters as well as in applicable guidance documents and regulations."

Repeated offenses may be a failure to look at the big picture and apply solutions across all systems and/or products, according to Schniepp. "Companies think in terms of solving the individual citation but fail to take that answer for change to a global look at fixing other processes and procedures

that might be susceptible to the same observation. Tunnel vision when responding to warning letters has a great potential to result in repeat observations," says Schniepp.

"Some of these 'repeat mistakes' are found to be violations of the same section of the regulations but stem from a different problem. Investigators tend to use repeat findings as a way to point to simplified trends that make one issue appear to be really bad, rather than the complex combination of issues that it truly is," Lynch says. "Some companies lack the staff, procedures, capability, and time to fully investigate and solve problems, so they pick something (e.g., a personnel error), close the investigation, and move on to release product, and the same issue reappears because it wasn't solved."

Cost can be another factor to repeated offenses, according to Moreton. "Often cost and/or short-term shareholder interests are used as an excuse to avoid some measures [to long-term change] … People complain that quality costs money, but if they really want to see how expensive things can be, they should try a consent decree."

DEVELOPING AND FOLLOWING WRITTEN PROCEDURES

The lack of written procedures and/or a quality unit is another frequent infraction identified in warning letters. From October 2016 through September 2017, FDA issued more than 400 FDA 483 observations for a lack of written procedures or written procedures that were not fully followed.[10]

Written procedures are key to a robust quality program, according to FDA and industry experts. FDA believes that the "most effective quality assurance (and compliance) strategies begin with robust internal procedures to adequately design and maintain a robust operation, and that can quickly identify and correct manufacturing problems when they occur."

What are best practices for developing written procedures for GMPs? While the agency does not endorse one particular approach to developing written quality procedures, FDA notes that these procedures should "be written to effectively communicate to the users of the procedure. FDA recommends that the style and format of procedures be accessible to users, as well as ensuring adequate coverage of its purpose. We recommend that the effectiveness of a procedural training program be evaluated to ensure that personnel learn and can follow the procedures as intended."

The trend in a failure to have written procedures is disturbing, according to Schniepp. She suggests that outsourcing quality, especially for start-up companies, may add to this problem. She questions whether outsourcing companies have the processes and procedures in place to handle new products. A robust sharing of information between client and contract manufacturing organization is also key, including product and process understanding. "We need to also remember

that new products, particularly in the biotech segment of the industry are novel in nature so the old way of doing business may not be applicable. Whatever the reason the industry must focus effort on making sure there are processes, procedures, and written instructions in place that support the release of product," Schniepp stresses.

Having all parties involved in the development of written quality procedures is necessary. "Including everyone affected by the procedure and writing the procedure with their input will result in streamlined and efficient procedures, which will be easier to maintain in the long run," says Schniepp.

Standard operating procedures (SOPs) written by people not familiar with the specific operation can cause disconnects, according to Lynch. "The best way to ensure adequate SOPs is to sit down with people most familiar with operations and map out the process steps and handoffs. This can be incorporated graphically using [swim lane diagrams] and similar tools like Visio (Microsoft) and include them as part of the document."

"In my opinion, in order to ensure that quality procedures are effective, it is necessary to involve those who know the process or operation being documented," Moreton agrees. "This may mean sitting down with the operator and finding out exactly what is being done and how, not what management thinks should be done and how they think the operation(s) should be carried out."

According to Schniepp, procedures should be mapped out, committed to paper, reviewed periodically, and updated as necessary. "Companies need to remember that their processes and procedures are not carved in stone and need to be changed to stay compliant with the operations being performed and the current interpretation of regulations," says Schniepp. New technologies and new product types may necessitate an update to procedures. Companies should be careful to not try and fit technology or product advances into current procedures but should instead take the time to review their processes and procedures and update them appropriately in responses to these advancements, she says.

"The best way to ensure adequate SOPs is to sit down with people most familiar with operations and map out the process steps and handoffs."

Consistent review of procedures is important, especially if a change in equipment, facility, or regulatory requirements has occurred, experts note. "Written procedures should be reviewed and updated as often as needed. However, if a process and procedure is being updated frequently then it probably wasn't very well written in the first place," says Schniepp. "This being said, procedures that are fairly stable should be reviewed at least every two years to make sure they are still current and reflective of regulatory expectations."

When developing written procedures, says Lynch, "each process and procedure should be tailored to its specific purpose, so they don't include unnecessary steps that add time to the process without applicable value to the procedure at hand."

Companies often lack details that will help operators understand the process, says Lynch. "The most important concept to remember when writing procedures is to include the detailed instructions for the operation or processes being defined by that procedure and not include extra explanatory or extraneous information that has no bearing on the operation or process being defined," agrees Schniepp.

IT DOESN'T HURT TO ASK FOR HELP

In warning letters, FDA commonly suggests the hiring of a third-party GMP consultant to help companies address their GMP deficiencies. Schniepp says these consultants can provide a "fresh perspective" when resolving GMP issues. "A new and fresh approach is valuable because the consulting firm has no preconceived ideas and can offer new insight to what may seem to be an old and uncorrectable problem," says Schniepp. These consultants can be helpful even when not suggested by regulators "because they are looking at the quality with eyes not steeped in the corporate culture," according to Moreton.

Consultants also have knowledge and expertise the company does not have. "[Consultants] can offer a variety of approaches and suggestions for remediating current problems as well as offering solutions to maintain and improving systems moving forward. One of the most important aspects to consider when hiring a consulting firm is to make sure they not only have the expertise, but they also have the time to devote to fixing the problem," says Schniepp.

When hiring a GMP consultant, Moreton suggests companies look at the experience of the contractor as a whole as well as the qualifications of the individual consultants "to ensure there is a good fit with the contractee's needs."

Lynch warns, however, that pharmaceutical companies should not rely too much on outside help. "Consultants can help companies get back on track if companies lack the resources internally. However, eventually companies have to sustain compliance themselves. Third-parties should provide expertise in the needed area and technology and have demonstrated success. Then, they should be able to teach and mentor personnel for improved behaviors and provide flexible models to fit company operations and culture. Usually, this is more than one-time training, but a program of measurement and support over time."

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Change Control for Standard Operating Procedures

The level of formality in change control may be holding back your SOP progress, according to Siegfried Schmitt, principal consultant at PAREXEL.

Siegfried Schmitt
Principal Consultant
PAREXEL

Q. We have one established change control process, and this process is applied to all planned changes, including changing standard operating procedures (SOPs). On average, it takes far too long to complete the process. For example, just preparing a line-by-line description of the rationales for each individual change in the text of the SOP can take several weeks. The result is that we often have to operate according to draft versions of SOPs, as changes must be implemented faster for operational or safety reasons. How can we expedite this process?

A: You have correctly interpreted the regulations, which require you to establish change control, or as International

Council for Harmonization (ICH) Q10 calls it, change management,[1] and to have documented procedures, most likely in the form of SOPs.[2] The issue seems to lie in the way change control is applied (i.e., the level of formality).

A formal change control process, which as you describe can take weeks or months to complete (e.g., for the replacement of a filling line), typically consists of these steps:

- Change request
- Feasibility assessment
- Technical review
- Input by regulatory affairs
- Review by quality assurance (QA)
- Approval of change
- Implementation of change
- Verification of change effectiveness
- Close-out of the change request.

Notwithstanding the formality of the process, a change control process should be effective,[1] meaning it is user-friendly, simple, and with minimal cycle time for decisions. This is aligned with the concept in ICH Q10 that the level of effort and formality should be commensurate with the level of risk.

Your example of preparing a line-by-line description of the rationales for each individual change in the text of the SOP gives a good idea of the level of formality you apply at present. A change to a SOP will be requested by the owner of the procedure covered by the SOP. So this

Courtesy of Spectrum Chemical Mfg. Corp.

person needs this change and is thus in a position to assess the technical and operational feasibility of the change very well. More importantly, the requester is perfectly well aware of the reasons (i.e., the rationale for each change in the document). For these reasons, it is standard industry practice to provide a summary rationale, not a line-by-line explanation in the revised document (e.g., change due to revision in the applicable regulations).

"There is no reason why a change to a SOP cannot be completed in a compliant, controlled, and formal manner in as short a time as one working day."

–Siegfried Schmitt

It is also easy for reviewers to see changes to the revised draft document as these are created with word processors in 'track changes' mode. This normally provides sufficient information for the reviewers and approvers. One issue often encountered at this step in the change process is the number of reviewers and approvers that have to sign off on the document. In effective organizations, this is kept to a minimum (i.e., two or three signatures).

VIDEO

Spectrum Chemical Quality Control

The solution to your problem is to review the level of formality applied, especially in the documentation of the change and the reasons for the change. There is no reason why a change to a SOP cannot be completed in a compliant, controlled, and formal manner in as short a time as one working day.

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