THE FOOD & DRUG LETTER®

Issue No. 800
July 18, 2008

Abstract: *FDA inspectors are focusing on the corrective and preventive action (CAPA) systems at regulated firms, and warning letters from the agency continue to cite CAPA deficiencies. Establishing and maintaining an effective and reliable CAPA system enables companies to comply with requirements and helps avoid negative FDA scrutiny. The agency's regulations are based on good laboratory practice (GLP), pharmaceutical good manufacturing practice (GMP) and device GMP regulations, and International Organization for Standardization (ISO) requirements. It is essential that companies identify current and potential problems, define solutions and show that the solutions are effectively corrected. A robust CAPA infrastructure follows the FDA's systems-based approach. The system needs written procedures outlining how information will be collected and analyzed, how problems will be investigated and what systems are in place to ensure appropriate actions are implemented. While manufacturers may have different procedures for different data sources, all sources of data must be fed into the CAPA system. The accurate and timely handling of data is central to a CAPA system. As is often the case when working with the government, education is a key factor, so this issue of* The Food & Drug Letter *focuses on CAPA systems.*

CAPA Systems Must Cover Numerous FDA Regulations

Although the methods and controls that are supposed to be used to package and store devices were around before the FDA's requirements were drafted, the medical device GMP regulations that continue to be the backbone of the requirements for the device industry were issued by the FDA in 1978.

The regulations state that there are three critical quality responsibilities for all regulated firms: identifying problems and potential problems, defining solutions to the problems and verifying that the solutions are effectively implemented.

The FDA regulatory requirements include the GLP regulations for nonclinical and laboratory studies; the pharmaceutical GMP and related regulations, such as those for investigational new drugs (INDs) and new drug applications (NDAs); and the device GMP regulations — also known as the Quality System regulations — that clearly state the elements of a CAPA system. It is upon these and the ISO requirements that the FDA's regulations are based.

From an FDA perspective, current views of CAPA are the same for all regulated industries. It is part of the systems-based approach that the agency routinely uses. This approach is evident in the FDA's comments and discussions relative to new regulations for the 21st century, and in many of the agency's

(See **Regulations** *Page 2)*

Regulations, *from Page 1*

initiatives and the kind of practical approach that the agency is taking toward inspecting companies and dealing with systems.

Its focus is on making sure manufacturers or developers of systems and products have good processes in place. It is important to recognize the movement toward process quality. Systems don't make products — processes make products. Examine your processes to ensure they are robust.

In 2002, the FDA announced a new initiative called Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century. In 2004, after two years of assessment, the agency released a final report on the initiative and a draft guidance for industry, "Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice." It says, "A quality system addresses the public and private sectors' mutual goal of providing a high-quality drug product to patients and prescribers. A well-built quality system should prevent or reduce the number of recalls, returned or salvaged products, and defective products entering the marketplace."

The guidance is not meant to replace the 1978 regulations. It is meant to help manufacturers meet the requirements of 21 CFR parts 210 and 211 in light of advances in manufacturing and understanding of current quality systems. The guidance also aims to harmonize cGMPs with other quality management systems outside the U.S. and with the FDA's medical device quality system regulations.

INSIDE THIS ISSUE

GLP Regulations Require Root Cause Identification

Even in a nonclinical laboratory setting, deviations from predicted results are expected to occur, and they must be documented and investigated. The fact that corrective actions are required implies that investigations must occur. Corrective actions require knowledge of the root cause of a problem in order to be effective.

The regulations at 21 CFR Part 58.33(b) and (c) say, "All experimental data, including observations of unanticipated responses of the test system are accurately recorded and verified," and "unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study are noted when they occur, and corrective action is taken and documented."

The FDA instructs, based on 21 CFR Part 58.35(b)(3), that as part of a study, manufacturers must inspect all laboratories at adequate and appropriate intervals. Several requirements must be met regarding those inspections, and the FDA then expects actions to be taken. In the GLP regulations, this is specific to a particular study. But it is similar to the concept of an internal audit or internal inspection.

Inspections are expected to look for and document deficiencies and deviations from regulations

(See **GLP**, *Page 3)*

GLP, *from Page 2*

and procedures, as well as to assure adherence to study protocols. There is a need to look for and evaluate quality problems and to implement corrective actions.

The regulations discuss failures at 21 CFR Part 58.63(b). Even equipment failures need to be documented, investigated and action taken to correct and prevent recurrence. They say the procedures for maintenance and calibration of equipment must "specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment."

The regulations also say, "Written records shall be kept of non-routine repairs performed on equipment as a result of failure and malfunction." The records "shall document the nature of the defect, how and when the defect was discovered and any remedial action taken in response to the defect" (21 CFR Part 58.63(c)).

The finding of deviations or deficiencies requires documentation, as well as corrective actions and corrections. The definitions from the FDA's training and interpretation say a correction takes care of a problem at hand, and a corrective action is done to prevent recurrence of the root cause of the problem. A remedial action is broad enough as a term to apply to both a correction and a corrective action.

According to 21 CFR Part 58.185(a)(9), the final report must include "a description of all circumstances that may have affected the quality or integrity of the data."

It is in the final report that the adequacy and accuracy of investigations into deviations, deficiencies and out-of-specification results are of utmost importance. To be valid from a scientific perspective, investigations of deviations or deficiencies must find a root cause that is clearly linked, through cause and effect, to the outcome.

CAPA Systems Must Be Documented

The pharmaceutical GMP regulations have requirements similar to those for GLP. The drug GMP rules say that quality control units shall "review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated" (21 CFR Part 211.22(a)).

The regulation is explicit that errors must be fully investigated, which means finding the root cause. The words in the medical device GMP are more explicit for CAPA systems. But the concepts also are built in throughout the drug GMPs.

The evaluation must determine the need for changes. These changes can be preventive or corrective. The rules at 21 CFR Part 211.170(b) say, "Any evidence of reserve sample deterioration shall be investigated in accordance with Sec. 211.192."

This section also clearly requires that data collection be adequate so manufacturers can perform trend analysis. The trend analysis can be focused on product controls and specifications, as explained in 21 CFR Part 211.180(e) and (e)(2). "Written procedures shall be established and followed for such evaluations and shall include provisions for … investigations conducted under Sec. 211.192 for each drug product."

Written records must be maintained so the recorded data can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures.

The theme throughout the regulations is that changes must be done in writing and documented. The evaluations also must be done per written instructions. That means manufacturers must have procedures and processes for conducting these kinds of evaluations and for detecting these

(See **CAPA Systems**, *Page 4)*

CAPA Systems, *from Page 3*

problems. The written instructions are supposed to include instructions for performing investigations. These are the primary CAPA procedures.

In the implementation of any quality system in its components, management's commitment to involvement is key. "Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 211.198, 211.204, or 211.208 of these regulations" (21 CFR Part 211.180(f)). Inadequate management responsibility is a commonly cited Form 483 deficiency in all FDA-regulated industries.

Batch Investigations

According to 21 CFR Part 211.188, "Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch."

It says in 21 CFR Part 211.188(b)(12) that the records should include "any investigation made according to Sec. 211.192."

Investigations are required — not encouraged — by the regulation.

Section 211.192 states, "Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed." The word "discrepancy" is one of the terms used to talk about nonconformity to specifications.

The regulation says, "The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up."

It is not enough to find the problem in one batch. Manufacturers have to look for downstream effects and see if the problems they detect are isolated or apply to other batches of the pharmaceutical product.

The requirement describes how an investigation is supposed to be done, as well as the need for a written record.

"Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with Sec. 211.192" (21 CFR Part 211.198(a)).

Complaints

Complaints have always held a special place within the FDA's GMP regulations. The agency gives high priority to this type of consumer feedback on actual and possible nonconformities. But not all complaints and nonconformities need to be individually investigated to root cause.

It is essential to know what the problem is, but each one won't necessarily be investigated once the solution is known.

All complaints need to be assessed to determine their validity and, if one is valid, whether it is already under investigation. Manufacturers must do enough work to determine whether an issue has been discovered or has been investigated thoroughly.

The regulation at 21 CFR Part 211.198(b)(2) states, "Where an investigation under 21 CFR

(See **CAPA Systems**, *Page 5)*

CAPA Systems, *from Page 4*

Part 211.192 is conducted, the written record shall include the findings of the investigation and follow-up. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with Sec. 211.180(c)."

A written record of the investigation is required; follow-up might include a correction or corrective action.

When an investigation is not done because a complaint is not valid, is already under investigation or is not deemed to be a high or moderate risk, for example, then the reason for not investigating, and who made the determination not to follow up and complete an investigation, must be documented in compliance with 21 CFR Part 211.198(b)(3). "Where an investigation under Sec. 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination."

Regulations Require Adverse Event Reporting

Manufacturers must notify the FDA of potential problems or adverse events — reporting is required. The issues listed in 21 CFR Part 314.81(b)(1) are all nonconformities that the FDA wants to know while deciding the fate of an NDA. Information about these nonconformities is supposed to be accompanied by an investigation into each.

For example, with regard to an NDA field alert report, the rules say, "The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within three working days of receipt by the applicant" (21 CFR Part 314.81(b)(1)).

The regulations require submission of "information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application" (21 CFR Part 314.81(b)(1)(ii)).

Drug GMP Requirements in R&D

Manufacturers should not forget the relevant application of the GMP requirements in R&D.

The GMP requirements clearly apply when operating under an IND. The IND regulations anticipate some changes in the chemistry, manufacturing and controls during the early stages of development.

Out-of-specification and failure investigation requirements clearly apply to the production of clinical trial materials (all phases of clinical development).

The FDA has modified some of this information for very early development work; previous GMP citations apply to products used to support an IND, NDA, new animal drug application or abbreviated new drug application. Although the product is not commercially marketed, an investigation still is expected — CAPA still applies. In fact, the investigations of out-of-specification results during these phases are what help improve, through corrective actions, the manufacturing formulation and even the packaging of the final drug product.

CAPA Subsystem Has Five Subsections

The FDA's CAPA subsystem is comprised of five subsections within CFR Section 820: corrective and preventive action (subsection 100), acceptance activities (subsection 80), nonconforming product (subsection 90), complaint files (subsection 198) and quality audit (subsection 22).

The FDA calls this set of issues the CAPA subsystem. The CAPA requirement at 21 CFR Part 820.100 forms a basis of the CAPA subsystem,

(See **Subsystem**, *Page 6)*

Subsystem, *from Page 5*

comprised of the requirements relative to the acceptance of incoming, in-process, finished and nonconforming products, and out-of-specification results, such as complaints and results of internal audits. Reasons for returns, results of audits of suppliers, production, environmental monitoring results and service records for a medical device are all data for the CAPA subsystem.

Medical devices also have three other regulations that are part of the CAPA system:

- 21 CFR Part 803 — medical device reporting is similar to the adverse drug event reporting process for pharmaceuticals;
- 21 CFR Part 806 — corrections and removal are separate from recalls, but are related; and
- 21 CFR Part 821 — medical device tracking requirements for implantable, life-supporting or sustaining medical devices.

Key Elements of an Effective CAPA System

The key elements and purposes of an effective CAPA program include systems to collect and analyze quality information, including feedback on procedures, processes and products, and systems to identify and investigate product and quality problems when they occur or might soon occur. The systems need to help determine why problems might have occurred and help manufacturers to perform thorough investigations about why situations might be leading to increases in, for example, a failure rate.

An effective program also includes systems to ensure that appropriate and effective corrective and preventive actions are taken. It is important to implement actions that will prevent reoccurrence of a failure or prevent the occurrence in the first place, even if there is only a potential for failure.

It is important to be familiar with the key terminology related to these systems. The concepts central to CAPA systems include:

- Correction — action taken to correct a nonconformity. This always is after the fact. A recall, for example, might be taken to remove a defective product from the market. That is a correction;
- Corrective action — action taken to eliminate or minimize the causes of an existing nonconformity to prevent recurrence. For example, there might be a process change to fix the process so that it no longer will result in a defective product; and
- Preventive action — action taken to eliminate or minimize the causes of a potential nonconformity to prevent occurrence. Action is taken to prevent something from happening that has not occurred.

CAPA Procedures Must Describe Data Flow

It is essential to establish procedures for a CAPA system, as well as sources of data. To the FDA, establish means define, document — either in writing or electronically — and implement. It means written procedures that have been properly reviewed, approved and are being followed by trained personnel. Those procedures and processes must be in place to have an effective CAPA system. It is important to feed all sources of data on nonconforming products and quality problems into the CAPA system.

The procedures should describe what the sources are, how the data are collected and by whom, and when and how information is routed to the CAPA system. The processes and procedures can be done manually or electronically. There can be separate procedures for collecting data and for evaluating a root cause.

Different investigation techniques are appropriate for different kinds of problems. The sources of information will vary but, at some point, all data with results of the investigation must flow into CAPA. Then, recommended and approved actions can be taken and

(See **Procedures**, *Page 7)*

Procedures, *from Page 6*

implementation and verification of those actions can be documented and tracked.

The procedures should be written to assure the data captured are complete, accurate and timely. Without this, investigations will not be complete and corrective or preventive action could be unnecessarily delayed, creating a bigger problem. The purpose of bringing the data together is to assist with trending of the data to detect existing or potential nonconformities. This is done both within the data source and across data sources.

For example, comparing electronic repair logs and the pieces of equipment that have been serviced or recalibrated in a given time frame with the in-process test results of product made in those pieces of equipment might show a potential situation for future failure. When equipment Y, for example, is within 30 days of its recalibration, in-process batches of drug product A usually are testing in the lower limits of the range.

Although there has not been a failure in the lower limits of the range, it might be wise to change the calibration schedule for equipment Y to prevent a situation where the calibration might affect the product if it is done late and might make it drop outside the range of acceptable product. This action would be preventive. It has not occurred. The preventive action might be to recalibrate more frequently. There are other preventive actions that might work, as well. One is not necessarily better than another.

Some normal CAPA data sources include:

- Process monitoring and control records;
- Acceptance activities;
- Incoming;
- In-process;
- Finished product;
- Environmental monitoring;
- Management reviews;
- Complaints;
- Returned goods;
- Internal audits;
- Out of specifications; and
- Equipment maintenance and calibration.

Servicing and maintenance are focused more on the device area. But these would apply to almost any kind of CAPA situation. The same responsibilities and expectations also are there for biological products.

Nonconforming product must be specifically controlled, and the controls need to be spelled out in written procedures. For clinical trials, nonconforming product still can be used for other purposes, not just in the trial itself, for example. For many nonconformities, an investigation to determine the root cause is required.

The extent of the investigation will vary depending on how many types of nonconformities for the product are known. For example, a mangled capsule is a nonconforming product. This type of nonconformity might be characterized by previous investigations. Therefore, each occurrence of this nonconformity is not required to be investigated if you can determine that the cause is the same.

Actual verification or validation of the actions that were implemented also should be documented in the CAPA system. There must be a mechanism for communicating a known quality problem or nonconforming product to those responsible for assuring the quality of the product or preventing such problems.

There must be communication capabilities to feed the information to those who can most effectively take advantage of it to prevent problems, to take corrective action or to make corrections in some cases.

Again, actions must be documented. Once the actions have been taken, implemented and verified or validated as effective, management should again be informed. This is usually done by trending reports during management reviews. It is essential that management be kept informed.

CAPA Tools for Nonconformities Must Be Validated

There are several automated electronic tools on the market that can make CAPA compliance simpler and more centralized. Tools can be used for collecting, investigating, documenting and tracking CAPAs for all types of nonconformities.

Many of these tools claim to ensure compliance with 21 CFR Part 11 requirements. Some of them have electronic signature capabilities. Some are heavily slanted toward pharmaceuticals, others toward devices. Some have a primary focus on GMPs; others are more generic and can be used in a GLP or NDA environment. Some are modules of larger integrated systems and can be used to generate a lot of other data that can be helpful in other ways, more than just the focused CAPA part of the system.

Many of these tools are classified as configurable systems, which have special meaning to the FDA. The configuration choices manufacturers make dictate how they will validate that system. Some of these tools are web-based applications. All have extensive reporting capabilities because it is the reporting capabilities that tell users where they stand relative to their problems and whether the problems can be resolved.

If any of the available tools become part of a computerized CAPA system, validation will be required. Validation is defined as, "Establishing documented evidence which provides a high degree of assurance that a specific system will consistently produce a product meeting its pre-determined specifications and quality attributes," according to the FDA's Guideline on General Principles of Process Validation.

How to Choose the Right CAPA Tools

It is essential for manufacturers to know what to look for in an automated tool and how to decide what is appropriate for their companies. Several questions and key points should be considered.

They should make sure a prospective system is compatible with existing software, with the network, with its operating system and with existing procedures, processes and sources. It is important to concentrate on these key points before buying any CAPA tool because it is essential to ensure the tool is compatible.

It is the manufacturer's responsibility to prove that the system complies with 21 CFR Part 11. The manufacturer must ensure the vendor can supply documentation that the system has been tested and was developed using good software development practices and should audit the firm itself.

The FDA does not require audits, but it might be wise for manufacturers to do an audit to

(See **CAPA Tools**, *Page 9)*

CAPA Tools, *from Page 8*

ensure good software development practices have been used in the creation of the tool. Manufacturers will be responsible for validating a new tool for its intended use. That responsibility includes validating any network that the tool will become part of, and, if it is web-based, that use of the web also is validated.

Claiming Part 11 compliance is an overstatement. Part 11 compliance is determined for an entire system as implemented in a facility. The most that the manufacturers of these tools can legitimately claim is that they have features that support Part 11 compliance, and manufacturers, then, would have the capability to use them in a compliant way.

Issues to Consider

What features are available to assist in assuring Part 11 compliance? They usually are well documented in the descriptions of the systems. How are those features documented and what documentation is provided? The manufacturer should find out what the vendor provides to show that it is Part 11 capable.

Is the system capable of being validated? Some systems may be difficult to validate. The system has to be validated according to the individual manufacturer's use. It cannot be validated off the shelf — only in a specific configuration. The only way manufacturers can validate a system like this is after they have configured it the way they are going to use it.

Can fields not in use be turned off? Some generic programs come with more fields than may be used. Some features allow the fields not in use to be grayed out or eliminated from the screen to avoid unintentional use. Sometimes if those fields are there, they can cause deviations from GMPs.

The operator's manual for software is a standard operating procedure (SOP), which manufacturers need to treat as one of their SOPs. The FDA would expect that manual to be adhered to unless it specifically is amended in a written procedure or process. Manufacturers should have a process that describes exactly how they will follow it, what elements they have chosen to use and what elements they have not chosen to use.

Is an audit trail of changes to entered data maintained? Audit trails are part of Part 11, but are also necessary to assure the CAPA system is properly functioning and utilized. Manufacturers must have audit trails because they must ensure data integrity, and the CAPA system has to have data with integrity in order to be useful.

The system should be easy to learn and to implement. Saying the system has to be easy to learn is not a clear requirement for a system that attribute cannot be tested. But training should be required as part of the purchasing agreement so manufacturers can make sure that employees learn the system properly.

Some systems come with a training and validation module. The training of existing and new employees should not occur in the live environment, but before they go live on the system. It is not always possible to do that, depending on the type of system.

Validation should be done in a separate instance that is identical to the actual system but not in a live environment, if possible. Manufacturers should not go live with a system that will not work and should not put invalid data or test data into a system that may later be hard to remove.

Trending needs to be done within and across data sources. Not all tools have the cross-data source-trending capability.

The report fields must be large enough to accommodate full reporting or allow attachment or references. How robust can the reporting be that is generated by the system? The raw data generated during an investigation should be kept in some manner with the investigation report, so manufacturers need to know how the raw data is being

(See **CAPA Tools**, *Page 10)*

CAPA Tools, *from Page 9*

handled by the system. During an inspection or an audit, even an internal audit, it is often necessary to go back to the raw data to look at the way the decisions were made. This is an important concept and something that is routinely used by auditors.

Does the system allow easy tracking, from the finding of an original nonconformity to verification of effectiveness of the implemented corrective or preventive actions? Manufacturers must be able to trace forward and backward to see the entire history of a problem. Reports should clearly identify the people involved in each activity. The FDA wants assigned responsibility — they want to see who made the decisions and performed the work.

Failure Investigations and Root Cause Analysis

The purpose of doing an investigation is to look for root cause. It also helps manufacturers identify what actions might be needed to prevent occurrence or recurrence, and it raises questions and challenges the process.

For example, if manufacturers distribute a product that has a defect, they must determine why it was distributed. If an investigation finds that quality control correctly identified the defect, but something happened and the lot was not quarantined as it should have been, they must find out why.

For example, they must make sure the warehouse personnel, who might not have quarantined the lot, have been trained in the quarantine and release procedures for the finished product. They should know what to look at and determine the lot status. Most firms stop at this point and retrain employees if that is what they find. But a good investigation will want to know why this lot didn't get into quarantine in the first place.

Such research might involve discussing the situation with warehouse personnel to find out what paperwork they receive with a lot. They may have had difficulty looking at the data and figuring out what it meant because they could not easily find where on this paperwork it was stated that the lot was quarantined.

Alternatively, research might reveal that few lots were quarantined, so warehouse staff were naturally going to put the lot into an area where it could be used rather than quarantine it. They also were busy doing many tasks, so, fundamentally, they let things slip. The best solution to prevent recurrence was found to be stamping the paper with a red inspection stamp saying "Quarantine" or a green stamp saying "Release." It might not be a bad idea to think about redesigning some documents to make them more easily understandable, too.

The purpose of a good investigation also is to assist in developing a clear, explanatory and scientifically defensible investigation report. This is a written record of what was done, why it was done and why specific actions were

(See **Investigations**, *Page 11)*

Investigations, *from Page 10*

recommended and taken. It can recommend solutions that don't have to be implemented.

The key objectives of investigations are:

- To determine if the observed result is valid. The beginning of most investigations, whether into complaints or out-of-specification test results, is to determine if there really is, or could be, an observed or reported nonconformity; and
- To determine the probable causes of the problem and potential impacts on tested products, other batches of the products and processes.

A good place for this to feed into is risk assessment. It is important sources of nonconformities are fed into risk analysis and the risk management process to take advantage of the concepts of risk mitigation and risk analysis.

The analytical nature of a root cause investigation helps identify obvious solutions. It also requires some investigation of recommended solutions to assure they are effective and to prevent occurrence or recurrence of a problem. It also helps assure there will be no adverse effects on the product or data.

Most investigations end with recommended corrections or corrective or preventive actions. The actions are then reviewed and evaluated by some level of management to decide which to implement. Management reviews — required by regulation in some cases and required by logic in most cases — are usually the place where these decisions are made and documented. Regardless, all actions or decisions not to take action should be documented in the CAPA system.

If a decision is made not to take a corrective or preventive action, that rationale and the identity of the person making that decision should be recorded. This documentation is done to make sure the proper decision was made and the proper level of evaluation is applied to problems to assure that appropriate corrective actions are taken at the appropriate time.

CAPA Includes Trending Requirements

It is important to know what and when to trend and the statistical methods that can be used. There are several requirements regarding trending.

The regulation at 21 CFR Part 820.100(a)(1) provides an extensive list of what should be trended, including "analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems."

For medical devices, the trending requirement is specific. The FDA says in 21 CFR Part 820.100(a)(1) that "appropriate statistical methodologies shall be employed where necessary to detect recurring quality problems." The device quality system regulation is explicit about what must be done and how to use statistics in analyzing CAPA data. The FDA considers something to be necessary unless a manufacturer can show scientifically why it is not. Manufacturers must be able to prove that they don't need to do something to avoid doing it.

For pharmaceuticals, although the word "trending" is not explicitly used as it is in the medical device area, the FDA considers it to be required by section 21 CFR Part 211.180(e): "Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures."

Trending should be done as often as necessary. For most products and processes, an annual review of trends is not enough. Most firms do a good job of trending complaints and monitoring results. But many of the other

(See **CAPA**, *Page 12)*

CAPA, *from Page 11*

CAPA sources are not trended often enough or are missed entirely.

The trending requirement at ISO 9001:2000 8.4, which is fairly straightforward and states exactly what the expectation is, says, "The organization shall determine, collect and analyze appropriate data to demonstrate the suitability and effectiveness of the quality management system and to evaluate where continual improvement of the effectiveness of the quality management system can be made. This shall include data generated as a result of monitoring and measurement and from other relevant sources … characteristics and trends of processes and products."

In regards to measurement, analysis and improvement, the requirement at ISO 9001:2000 8.1 states, "The organization shall plan and implement the monitoring, measurement, analysis and improvement processes needed … [and] shall include determination of applicable methods, including statistical techniques, and the extent of their use." This trending requirement makes a reference to statistical techniques and expectations.

Feedback Sources Are Internal and External

The sources used in trending are extensive. Information for CAPA comes from both internal and external feedback sources. Sometimes what is internal and what is external is an arbitrary division. The most important consideration is not to miss anything.

Internal sources include:

- Inspection test data, in-process data, final inspection test information, quality assurance unit inspection findings, scrap and yield rates and process control data. There are a lot of things on which manufacturers routinely test and collect information. Internal feedback sources include all of these things, as well as finished product testing, processes and environmental control data, data regarding scraps and defect rates. All of these things can be very important in yielding good internal data;

(See **Sources**, *Page 13)*

Sources, *from Page 12*

- Incoming inspection data collected relative to a part number, supplier, batch or lot number. These things, although they might be relative to products that come from the outside, are also parts of the internal data sources. In addition, equipment maintenance and calibration data can be valuable in understanding processes. They can make it possible to identify and prevent some nonconformities. Internal audits also are a great source of information; and
- The various reports and records generated during manufacturing, packaging, labeling and employee training — those that are used to make changes and those that are found relative to nonconforming materials. They include records on device history, drug batch, training, change control, rework (reprocessing) and nonconforming material.

External feedback sources can come from several different places. They include:

- Complaints. When the FDA talks about complaints, it is very expansive. The agency talks about complaints from consumers and employees; through various systems like Medwatch, MDR, Drug Adverse Event Reports and field service reports relative to products; and from product returns or journal articles. Sometimes employees can define things that would be handled as an external source; and
- Legal claims, warranty issues and claims, regulatory audits and client audits. Companies sometimes forget legal claims and warranty claims. They don't include these because they are generally handled in a different way than a normal complaint or problem would be, and sometimes they don't make it into the CAPA system, but these are also external CAPA data sources.

What and When To Trend

It is not easy to decide what to trend and when to trend it. Tendencies are to rank products from major to minor. Companies identify what is an important trend and what is not so important, or might not even be a trend.

It is important to select items with major impact to the business, especially when related to product and process. The FDA focuses on three areas of risk: patient risk, first and foremost, directly affecting the patient; product risk — not producing a bad product; and process risk. Manufacturers should go from top to bottom, focusing on those key areas.

Prioritization is critical. Start at the top, looking at areas with a lot of impact and go to the bottom for issues where there would be less impact. Address all of the areas eventually, but there is nothing wrong with tracking and addressing the top issues, so long as catastrophic problems are not neglected. The key is to trend every data source, not just the top ones. Some companies have a tendency to leave things open too long without decisions. Once the problem is solved, the company should go back and close the data and the collections parts, saying that the issue is resolved. Documentation of closure is critical.

When and the extent to which trending is done depends on the impact of the issues. Risk and impact are the way to evaluate and determine how frequently trending is done and whether an area makes it to the top of the list. The elements that offer insight into major risks are best trended first and most often. Complaints, for example, often constitute an area that deserves focus, even if some of them are not particularly major, because they deal directly with patients — the area of risk the FDA focuses on.

Statistical techniques are used to detect recurring or potential quality problems within and across data sources. It is important to use tried

(See **Trend**, *Page 14)*

Trend, *from Page 13*

and true statistical techniques when evaluating products and assessing risk. Some of the statistical methodologies include Pareto charts, run charts and control charts.

Pareto charts summarize and display the relative importance of the differences between groups of data; control charts focus on the variation in a process; and run charts, which are similar to control charts, focus more on time patterns, displaying process performance over time.

There is no need for manufacturers to be elaborate. They should look across data sources, as well as within the data sources, for trends. They should also look at relationships. Failures in one area also may be seen in failures in another area.

Management Reviews Make Good Business Sense

Eventually, management must review all of the data trends. The trends should be reported so that management hears first about those that occur most frequently, as well as those that pose or represent the greatest risk to the company, the products and the processes but, first and foremost, to the patients.

Anything that threatens data integrity should be considered a very high risk. Companies produce two products in the regulated environment — data and the products they try to sell. Both of those are key.

Management review is expected to be conducted periodically. Annually is not good enough. How often is enough? The idea is to establish a level of frequency that is based on the kinds of problems being detected. In going through and looking at the nonconformities that can be identified, levels of risk must be established.

Manufacturers should look at what the risks truly are and, based on the risk levels, consider more frequent meetings and more frequent reviews — and try to address these more rapidly.

They need to make sure that not only nonconformities, but also trends in causes are reviewed. Some trends are reviewed as part of investigation processes, to help decide what corrective or preventive action or even corrections to take. Other trends are reviewed to help management representatives explain to management with executive responsibility how the quality system is performing.

How healthy is the quality system? Management must assure that each corrective or preventive action that is taken is appropriately implemented and verified or validated. The process should include identifying problems, recommending solutions and verifying that those solutions fix the problem.

The key is that management must clearly know what the top-level problems are and must know what is being done to deal with those top-level problems. The company has to be able to demonstrate that it is being effective. That is not just for the FDA or regulatory reasons, that is also just for good business practice. Problems cost money. The quicker manufacturers can resolve them, the better off they are.

FDANEWS

Customer Service
(888) 838-5578 • +1 (703) 538-7600
customerservice@fdanews.com

Editor: Lauren Lentini
(703) 538-7663
llentini@fdanews.com

Ad Sales: Andrew McSherry
(703) 538-7643
amcsherry@fdanews.com

Content Sales: Alka Desai
(703) 538-7669
adesai@fdanews.com

300 N. Washington St., Suite 200 • Falls Church, VA 22046-3431 • Phone: (888) 838-5578 • +1 (703) 538-7600 • Fax: +1 (703) 538-7676
www.fdanews.com

Reporters: Martin Gidron, Christopher Hollis, Elizabeth Jones

President: Cynthia Carter; **Publisher:** Matt Salt; **Editorial Director:** David Grant