



INSIGHTS

Preparing for Changes in FDA Guidelines: A Fresh Approach

By Carol Brandt

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Executive Summary

The Federal Drug Administration (FDA) is changing, and the pharmaceutical industry needs to be aware, prepared, and change accordingly. Recent publications indicate a change in strategy for inspections with a risk-based approach. The risk-based approach is not only applied to the inspection process, but also expected to be applied by the industry in the design, development, and manufacture of drug products. Effective Quality Systems must support and control this approach and the ultimate safety of our drugs.

The recent report published by FDA, “Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach,” (herein The Report) addresses a host of different subjects, from internal FDA changes, to the effects of those changes on inspections, as well as the need for implementation of new technologies and manufacturing quality goals. CAPA (corrective and preventative actions) in the sense of “corrective action” is a starting point, but the ultimate goal is continuous improvement. Proactive, preventative measures versus correcting the problem after it has already occurred introduce new ways of thinking. Many of the industry manufacturers are just implementing new, automated CAPA systems to replace unreliable, manual, and multiple systems, and the hurdle to address continuous improvement may seem quite arduous.

Can we respond to a new strategy? Can it improve our quality and business goals? Does it make sense to be proactive? Absolutely! Now the question is: what can we do when we only have an introduction to the changes coming, before the supporting guidelines and regulations are published?

What changes are coming?

In September 2004, FDA (CDER) published its Final Report, “Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach,” describing an innovative approach to inspections and quality awareness for the pharmaceutical industry. It is a fairly lengthy document and one that should be read with a key understanding of the primary issues facing FDA today and their plans for a new strategy.

Recent FDA accomplishments and the development of a new framework are discussed in The Report, as well as plans for enhancing FDA’s regulatory programs and facilitating the use of new technology in the control, quality, and manufacture of pharmaceuticals. The recent publications describing the establishment of the Process Analytical Technology (PAT) initiative are summarized, which outline a systems perspective and facilitate the introduction of new technologies to the de-

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sign, development, and manufacture of drug products. This includes human and veterinary drugs as well as human biological products, and the specific mention of vaccines.

Although several issues are presented, many of which impact internal FDA awareness, cooperation with international regulatory partners, training and management of inspections, some readers may be quick to put The Report aside and wait until further guidance information is released. All of these issues, however, impact the industry.

It should be noted that the approach to risk management and Quality Systems described as FDA internal/inspectional changes can and will be applied to the manufacturer internal processes as well. Continuous improvement and risk management are highlighted repeatedly. There are, however, three very key preventative compliance areas, which can and should be addressed immediately by the pharmaceutical manufacturer:

- Quality Systems Status and Control
- Process Control Acceptance Levels
- Proactive Approaches to Ensure Sterility

Quality Systems Status and Control

Quality Systems regulations define a common sense approach to control and a manufacturer's assurance that GMPs (Good Manufacturing Practices) are being followed, tracked, and trended. Keeping track of the problems, acting on the solutions, and determining the root cause just isn't enough. This can become a difficult cycle to break. Improvement of the process is essential to breaking that cycle. It's all about evaluation and prevention, rather than repetitive action to correct the same problems.

In previous CAPA white papers, we have said that mistakes happen every day—the wrong amount of an ingredient is added to a drug product; an employee is lax on training and doesn't gown properly; a Standard Operating Procedure isn't followed. It isn't good enough that mistakes are caught—they need to be tracked, trended, and *prevented*. Not tomorrow, but **now**. They don't even need to be mistakes, they can be “near misses”; enough to cause concern. Mistakes and near mistakes can be costly to the manufacturer and, if gone unchecked, can pose a health risk to the public. Whether an injectable sterile drug or medical device, pharmaceutical pill, blood component or vaccine, control is the responsibility of the manufacturer and begins with the raw material vendor and ends with the final distribution of the product.

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Throughout the industry, CAPA systems are being improved and automated. CAPA is the term coined to describe the method of documenting, tracking, and trending errors or deviations from the normal process as a means to prevent future occurrences; it establishes a quality policy defined by systems. A CAPA program can only be successful if it is utilized routinely and monitored. Problems and trends must be quickly identified and remediated. Now, that isn't enough.

Take a look at the monthly CAPA report that your department or group generates. Are problems truly acted on in a timely fashion? Are resource issues commonly used as excuses for delay in the correction of a problem? Can you admit to assigning a cause that just meets the requirement of reporting it, and wasn't really researched as well as it could have been? If so, can we ever get to a state of *continuous improvement*? And, what does that really mean?

The basic CAPA system is essential in tracking the problems, but acting on them and taking it one step further to be in the realm of "continuous improvement" is much more difficult. For those who have not developed an automated or efficient manual CAPA system by now, be forewarned. For those who have not developed a centralized database or method for QA review of all CAPA issues, be forewarned.

Today, many companies are doing a great job of listing the problems, assigning them to someone who has another full-time operational job, and lending little time to ensuring that problems are in fact reviewed by QA, corrected, and remediated in a timely fashion. Delays in action, and failure by QA to review problems by area or statistical occurrence, can cause problems to occur again and again before the root cause is identified and corrected. In fact, the root cause may never be correctly identified if the connection of like problems in different areas cannot or is not made.

Here are some suggestions:

- Review your Quality Systems. Take a systematic approach, starting with facilities. Track your Quality Systems and methods of documentation and review, and evaluate their efficiency, effectiveness, and robustness throughout the product lifecycle, all the way through release and distribution.
- Evaluate your ability to identify "like" problems and establish a root cause.
- Assess your ability to act on problems quickly and remediate them.
- Ensure you have a statistical reporting of the problems and their occurrence.

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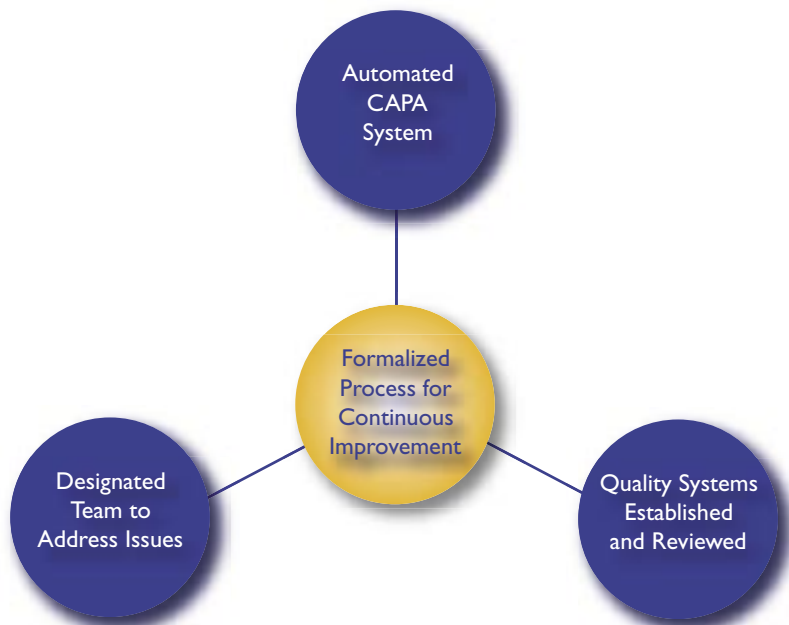


Figure 1. Pro-Active Manufacturer

Once you have established that your basic Quality Systems are sound and your CAPA system is effective, work towards continuous improvement by:

- Evaluating and defining your high-risk areas. The Report defines efficient risk management as the use of the “best scientific data, development of quality standards, and use of efficient systems and practices that provide clear and consistent decisions.”
- Establishing methods to measure, control, and predict quality.
- Evaluating processes to ensure a state of control can be achieved and maintained.
- Formalizing an on-going and continuous improvement initiative.

Process Control Acceptance Levels

Is a process really “in control?” When is a result “good enough?” Is it good enough to establish limits and ranges and just barely make it? How much variability is acceptable? How often do we go back to look at how the limits were established and whether or not they continue to be scientifically valid? We remain comfortable with our current state, and The Report gives us an indication that we don’t often evaluate a “desired state,” but are more apt to maintain the current, comfortable state.

Processes should be continuously evaluated to reduce variability. This is not a stagnant set of specifications, but rather one that changes with the change control rate of the process. New support systems, equipment, and instruments may be added, all of which can affect the variability of the process. Continual evaluation and improvement of acceptance levels throughout the process are critical to the control of that process.

Intimate scientific knowledge of the process and its components supported by data will establish a scientific basis for controlling the process. The more that is known about the process and supported with scientific data through testing controls, the more solid the basis one has for establishing appropriate limits and

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acceptable variability. This lends itself to the establishment of proven process characteristics. Typically the knowledge base in this area is increased through the use of various statistical techniques.

Along with scrutiny of existing Quality Systems and opportunities for improvement, the drug process should be reviewed for efficiency and areas where wasted efforts can be eliminated. Once again, the process should include the entire drug lifecycle, from design through marketing. The “desired state” should be the basis for the evaluation, which is a difficult mindset, at best. All too often we are apt to try to improve the current state because we are comfortable with the predictability, rather than consider major changes that would bring our technology and scientific process to a “desired state.”

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Consider a fresh approach. Consider your staff and whether or not they are capable of looking at the process in an innovative way. Reengineering of business strategies is common in the industry. We spend significant parts of our budgets to ensure that our businesses operate with state-of-the-art enterprise resource planning systems, and that inventories are under control and anything affecting revenue is tightly controlled. Reengineering of overall processes such as supply chain is scrutinized for improvements. It is rare, however, that we commit the same time and budget to evaluate individual, established drug processes.

Proactive Approaches to Ensure Sterility

Key to the FDA’s concern is sterility assurance in pharmaceutical, biological, and veterinary drugs and vaccines. This certainly has and should be a primary concern, but recent sterility problems in the industry have led inspectional agencies to highlight change and a proactive approach as a solution to improvement. The Report asks the industry to consider a different strategy.

- “Ensure robust product production through adequate design and control of equipment and facilities.”
- “Ensure that the operational and raw material inputs are predictable through adequate quality control and quality assurance.”

What can we do to meet the basis of these statements and be as proactive as possible? Note the repeated use of the word “control.” Are we controlling or just maintaining the current state? Are the controls we have in place “good enough?”

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The innovative proactive manufacturer defines a program for continuous improvement, rather than simply tracking and responding to the problems.

The basis of sterility is contamination prevention, and the methods of measuring contamination are limited by the standards we set. Sterility assurance is only as good as the specifications and ranges established for gowning, testing, facility, fill room, environmental monitoring, fungi, bioburden, particulates, product holds, and corrective action items as examples. Evaluation of every limit, specification, and excursion, for every indicator of sterility, should be performed. Raise the bar—consider whether or not the specifications are the best they can be or just “good enough.” Look at the original scientific basis for the excursions. Have they changed? Can we set a higher standard? If your data are consistently near the lower end of the specification, consider adjusting the specification range to lower the limit. A thorough evaluation of the processes involved in the entire product lifecycle should be reviewed and scrutinized with appropriate documentation indicating the completion of the review.

Summary

The same theme runs throughout each of the three areas cited in The Report:

- Quality Systems Status and Control
- Process Control Acceptance Levels
- Proactive Approaches to Ensure Sterility

Taking a fresh look at Quality Systems, process control and sterility assurance throughout the product lifecycle is the primary message for proactive manufacturers; creating a controlled environment through the establishment of a continuous improvement program.

Quality Systems are the shared goal of regulated industry firms and FDA, and the basis for addressing all three key issues. The word no longer just defines a “good” approach. Industry standard now defines Quality Systems to represent specific areas of manufacturing requiring system control:

- Management Control
- Design Control, Corrective and Preventive Action
- Production and Process Control
- Facilities and Equipment Control
- Materials Control
- Documents/Records/Change Control

FDA has established requirements for Quality Systems in the regulations. Guidelines for development and implementation of compliant systems are gleaned

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from industry “best practices.” CAPA systems, allowing a centralized method of tracking and trending OOS results, complaints, deviations, and adverse events, represent the state-of-the-art solution to provide the information rapidly and assist in maintaining control and preventing problems.

Taking this one step further by defining a program for continuous improvement, rather than simply tracking and responding to the problems, is the innovative mindset of a proactive manufacturer. •

Clarkston Consulting is currently conducting a survey of Pharmaceutical executives highlighting how they are preparing for and anticipating the new risk-based guidelines. The results will be shared with the participants. If you’d like to participate, please contact Laura Polas at 1-877-331-1900.

Primary Reference

“Final Report—Pharmaceutical cGMPs for the 21st Century—A Risk-Based Approach,” CDER, Food and Drug Administration, September 29, 2004.

Secondary References

Following is a summary of guides, manuals, guidances and regulations, which should be reviewed as a basis for review/improvement efforts:

FDA Staff Manual Guide, “Quality Systems Framework for Internal Activities”

Draft Guidance for the Industry, “Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations”

Final Guidance for the Industry, “Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Process”

Manufacturing Science White Paper, “Innovation and Continuous Improvement in Pharmaceutical Manufacturing”

About the Author

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About Clarkston Consulting

Clarkston Consulting is a nationally recognized management and technology consulting firm that provides validation, compliance and implementation services to address issues that its clients face in FDA-regulated environments. Nearly half of the top 50 pharmaceutical companies in the world have worked with Clarkston's consultants, who deliver award-winning expertise and exceptional customer satisfaction. Clarkston Consulting's approach focuses on the key business drivers aimed to improve productivity of product development pipelines; communications between sales, marketing, and customers; and business processes centered on new product launches. To learn more about Clarkston Consulting, visit www.clarkstonconsulting.com/whitepapers.



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