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# OTC Drugs: Manufacturing, GMP and Quality Management

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The CGMP regulations for drugs contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug product. The regulations make sure that a product is safe for use, and that it has the ingredients and strength it claims to have.

The approval process for drug marketing applications includes a review of the manufacturer's compliance with the CGMP. FDA assessors and investigators determine whether the firm has the necessary facilities, equipment, and ability to manufacture the drug it intends to market.

cGMP guidelines are applicable to the complete product lifecycle, from raw materials and components up to the finished product, including its discontinuation. FDA has “strongly recommended” engaging a third-party consultant qualified in the relevant regulations to assist in meeting CGMP requirements.

The first step to implementing a cGMP-compliant QMS is understanding what cGMP compliance means. cGMP regulations address several operational aspects, including personnel qualifications, sanitation, equipment verification, process validation, and record keeping.

## Regulations and Standards

Regulating bodies expect manufacturers to know and follow the standards. For firms manufacturing drug and health products, 21 CFR Parts 210 and 211 as well as any relevant USP standards governing specific types of products should be followed.

Part 210 - An outline of the minimum GMP requirements covering manufacturing, facilities, and controls for the manufacture, processing, packing, and holding of all drugs in such a way that meets the guidelines for safety, quality, and purity. Part 211 - An outline of the minimum GMP requirements for finished drug products. This also covers various other areas, including personnel, facilities and equipment, production processes, stability testing, and labeling.

The rules in the entire 21 CFR 200 series explains handling, storage, labeling, processing, donor selection and a host of other elements relevant to the pharmaceutical marketing process, they impact both manufacturers and the firms they partner with to produce and market products, including suppliers and contract manufacturers. Companies who want to sell their products in FDA-regulated markets must be willing to apply compliance and quality assurance efforts to every part of their supply, manufacturing, and distribution chains. Specific to many OTC manufacturers, a review of current systems and processes will often reveal significant deficiencies. While prior regulatory encounters are obvious indicators that systems require improvement, all firms should take it upon themselves to assess their functional understanding and adherence to 21 CFR 200 series regulations and make any necessary improvements as a proactive compliance initiative.

## CGMP or QMS Problems

The increased inspection activity at OTC and similar manufacturing sites is driven primarily by deficiencies that are being observed over and over again. Nearly all of these problems point to a QMS in need of improvement. When considering the health of the QMS and where certain vulnerabilities may lie, existing warning letters can serve as helpful resources for assessing own susceptibility to deficiencies regulators have observed at similar firms and are likely targeting during inspections.

QMS failures which reveal themselves in areas like water system management are susceptible to problems that can be incredibly serious while being frustratingly difficult to detect without proper quality assurance measure if investigators detect a water system failure only to discover a firm isn’t identifying the microbiological contaminants,

it's likely that upon pulling and testing their own sample, they could identify a highly dangerous contaminant that could compromise consumer safety, thereby revealing a major QMS gap. In a situation like this, a robust QMS would have provided documented processes and procedures for providing the data needed to not only detect the specific contaminant but correct and prevent the problem when it was discovered. Without it, firms are forced to jump directly into correction mode without the information they need to be successful. As time goes on, failing to accurately capture the nature of the problem at the outset only makes matters worse when responses are rejected citing inadequate problem-solving methods.

## Testing and Calidation Methods

Microbiological method development is often mishandled or overlooked entirely. Method suitability and validation processes are complex, often involving wide specifications, broad parameters, and the inherent variation that comes from working with living organisms. Method suitability testing is used to evaluate residual antimicrobial activity of a product under testing to ensure that the results achieved in recovery test media are representative. Regulating bodies like the FDA expect firms to produce a method of testing that effectively neutralizes any antimicrobial effect and will allow control organisms to grow in expected numbers. Products likely to have this type of effect may contain preservative agents, anti-microbial or bacterial or fungistatic compounds. Conducting these activities properly requires strict adherence to criteria set out in USP guideline. It is absolutely critical to have the appropriate comparison controls in place to ensure method development is properly carried out and the optimal technique is used.

## Non-conformances and CAPA

Regulators expect firms to understand and use CAPAs as improvements to processes and procedures that eliminate non-conformances based on the results of root cause investigations. Once the root cause is determined, a corrective action is identified and implemented into the process. The change is then monitored to determine if the proper root cause was identified and if the corrective action was effective. Sometimes, the root cause analysis may reveal a potential for situations that may result in a compromised product. The solutions implemented to prevent predicted non-conformances are preventive actions. While there are many perspectives on what makes for a successful CAPA system, just about everyone agrees that one of the most critical points is the initial investigation into the nonconformance to determine the root cause, or root cause analysis. To conduct a thorough root cause analysis, teams should be qualified to use analysis tools that enable them to examine the impact of process inputs and their effect on the nonconformance. Once the investigation logically hones in on the true root cause, a CAPA can begin.
Checklist when evaluating the CAPA processes for compliance with FDA regulations is:

1. Verify that CAPA system procedure(s) that address the requirements of the quality system regulation have been defined and documented.
2. Determine if appropriate sources of product and quality problems have been identified. Confirm that data from these sources are analyzed to identify existing product and quality problems that may require corrective action.
3. Determine if sources of product and quality information that may show unfavorable trends have been identified. Confirm that data from these sources are analyzed to identify potential product and quality problems that may require preventive action.
4. Challenge the quality data information system. Verify that the data received by the CAPA system are complete, accurate and timely.
5. Verify that appropriate statistical methods are employed (where necessary) to detect recurring quality problems. Determine if results of analyses are compared across different data sources to identify and develop the extent of product and quality problems.

6. Determine if failure investigation procedures are followed. Determine if the degree to which a quality problem or nonconforming product is investigated is commensurate with the significance and risk of the nonconformity. Determine if failure investigations are conducted to determine root cause (where possible). Verify that there is control for preventing distribution of nonconforming product.
7. Determine if appropriate actions have been taken for significant product and quality problems identified from data sources.
8. Determine if corrective and preventive actions were effective and verified or validated prior to implementation. Confirm that corrective and preventive actions do not adversely affect the finished device.
9. Verify that corrective and preventive actions for product and quality problems were implemented and documented.
10. Determine if information regarding nonconforming product and quality problems and corrective and preventive actions has been properly disseminated, including dissemination for management review.

## Root Cause Analysis Methodologies

**Fault Tree Analysis (FTA):** This is a deductive procedure used to determine the various combinations of hardware and software failures and human errors that could cause undesired events (referred to as top events) at the system level.

**Fishbone Diagram:** Also called a "cause and effect" or "Ishikawa" diagram (among others), a fishbone diagram is a visual tool for looking at cause and effect. A problem or effect is displayed at the the "head" or "mouth" of the fish and possible contributing factors are listed on the "bones" under various cause categories. These models work best when the "head" of the fish contains a very detailed problem statement. This helps eliminate scope creep of the team's discussions. What happened? When? Where? These can help narrow the focus to solve the problem.

**5 Whys:** The 5 Whys is the simplest technique for root cause analysis. It can be very effective when answers come from people who have hands-on experience in the process being examined. It is remarkably simple: when a problem occurs, you drill down to its root cause by asking "why?" five (or more) times. Then, when a countermeasure becomes apparent, you follow it through to prevent the issue from recurring.

Corrective and preventive actions should always be utilized when necessary throughout any area of the organization. Given this very important point, it's also helpful to know which systems typically give rise to the problems CAPA is used to solve (and prevent). While again, these are by no means the only areas to expect issues to occur, it can help prioritize regular monitoring and realize the true scope of problems by identifying their early indicators.

## Quality Unit

The pharmaceutical Quality Unit (QU) has been the target of many warning letters to OTC manufacturers and similar firms as an underlying cause of product quality and CGMP compliance problems. Multiple OTC firms have been cited for having an inadequate QU, sometimes lacking one at all. Similarly, regulators have also cited firms for a lack of written procedures that govern the responsibilities and functions of the QU, whether they have one or not. 21 CFR Part 211 is clear about the need to establish a "quality control unit" with the documented responsibility and authority to make critical decisions. The lack of a QU or inadequacies within an existing unit typically come attached with a direct recommendation to engage third-party experts.

## Inspection History

A firm's prior inspection history can provide a general guide for managing expectations and inferring regulatory interest in areas that may have required attention in the past. If a firm received inspectional observations in the past, it's imperative to review what actions have been taken to remediate and resolve those issues and ensure everything is thoroughly documented. Similarly, firms that have received repeated observations should pay extremely close attention to the underlying quality system failures that led to them.

## Conclusion

cGMP compliance demands a commitment to continuous improvement. cGMP compliance can be achieved by regular review meetings, customer feedback, and robust CAPA systems.

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