



# A Scientific Approach to Good Manufacturing Practices

**As technology progresses and manufacturing regulations evolve, manufacturers need to challenge previously accepted procedures to become a model for best practices.**

WHITE PAPER

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By scientifically affirming every decision and by embracing integral approaches to quality, contract manufacturing organizations (CMOs) can reduce regulatory risk and become a leader in developing best practices meeting current Good Manufacturing Practices (cGMPs).

Contract Manufacturing Organizations (CMOs) represent an important and growing industry involved in the manufacture of active pharmaceutical ingredients (APIs) and drug products in a range of dosage forms. By nature of the end use of their manufactured goods, CMOs come under the oversight and responsibility of federal agencies in multiple regions and jurisdictions. These agencies use inspection and enforcement actions to ensure quality compliance and meet their responsibility to protect the public. As quality best practices continue to evolve and improve in response to technology and process advances, as well as in response to public health incidents, federal agencies have continued to challenge the industry to improve its quality compliance and mitigate risk of future incidents occurring. As a result, CMOs exist in an environment of continuous improvement and evolving quality standards that are a requirement of their existence.

The role of the quality unit is to ensure that the various operations that exist throughout the entire product life cycle are appropriately planned, approved, conducted, and monitored to quality standards. A robust, risk-based quality system must be developed and managed by the quality unit to ensure these standards are met. A good quality system will allow for the effective assessment of whether a process or manufacturing system (i.e. production, packaging and labeling, materials, facilities and equipment, and laboratory controls) is in a state of control. When a part of the process or manufacturing system is identified as being no longer in a state of control or trending in that direction, then the quality system will require that appropriate corrective and preventive action (CAPA) is implemented. Often, new findings, advances in technology, best industry practices or new FDA focus efforts may mean that what was once a state of control may be no longer be acceptable.

By adopting a complete approach to corrective and preventive action (CAPA) initiatives, CMOs can help to ensure compliance and quality assurance for their clients and prevail as the standard for current best practices industry wide. In order for outsourcing to remain a viable strategy in helping pharmaceutical companies remain competitive, CMOs must place highly trained and qualified quality and technical or operations individuals at the helm of process improvements and quality system modernization. By continuously implementing CAPAs into an organization's quality systems, contract manufacturing organizations can build a stronger and more flexible organization equipped to deal with the cutting edge of industry quality standards.

### Keeping current by making informed decisions

US Food and Drug Administration's (FDA's) current Good Manufacturing Practice (cGMP) regulations as written in the Code of Federal Regulations – for example, 21 CFR parts 210 and 211 – contain explicit requirements for the manufacture of finished pharmaceuticals. APIs and drug products must be manufactured in accordance with cGMP. The Code of Federal Regulations lists these tenets, as well

as specific requirements, for a firm to uphold and follow in order to manufacture products in accordance with cGMP. The “c” stands for “current” because it is understood that good manufacturing practices are not a static concept. Instead, they must be defined in relation to current insight and regulatory expectation brought on by technological advancements and collective lessons learned, and best practices developed, within the industry. Recognizing cGMP's dynamic nature, the CFR and its associated FDA Guidances are regularly revised in order to remain current. Because of this context, it is critical that firms continuously assess their quality systems and operations against what can be considered as “best practice.” An important component of this assessment is the need to continuously monitor literature and other sources of documentation, and utilize external training, outside consultants or other external meeting attendance opportunities. In a culture of continuous improvement, being aware as much as possible of external developments is critical to remaining near the leading edge.

Regulations are not a specific set of instructions, but are written with broad enough applicability so as not to be overly prescriptive and otherwise thwart innovation, technological advancement or operational improvements and efficiencies. As such, following the Regulations and implementing best practices in accordance with cGMP's leaves opportunity for interpretation. The danger is that an interpretation can be executed in a way that falls short of upholding the spirit and principle of the regulation, and many organizations have fallen into this trap and suffered significant operating disruption. To become a model for cGMP and avoid as much as possible the risk of coming up short, manufacturers should focus on implementing a system in quality that scientifically can substantiate each decision. This includes decisions with the way a quality system is structured, the way a manufacturing organization executes to that quality system, and the way a process is designed.

In order to get to and remain near the leading edge for current best practices, food, drug, and cosmetic manufacturers must establish and maintain a healthy quality system that promotes continuous improvement as a function of an organization's risk management and CAPA initiatives. The FDA continues to critically challenge previously accepted industry manufacturing practices to rightfully ensure the protection of the public as much as possible. The FDA is favoring scientifically substantiated practices, wrought out by risk consideration and management, compared with those formerly deemed standard industry practices. cGMP regulations are communicated by FDA under the authority of the Federal Food, Drug, and Cosmetic Act.

An effective quality risk management approach, conducted in accordance with ICH Q9, can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing.[2] Best and current practice is arrived at when effectively implementing those practices that are feasible and valuable.

Evolving technology and regulatory expectation compels organizations to regularly reassess what is in fact feasible. The decision to implement what is feasible will depend upon whether or not it adds value insofar as it contributes to the safety, identity, strength, purity, and quality of the product.<sup>[1]</sup> In order to best identify what is feasible and valuable a firm needs to perform effective risk assessment of the given process, system, or program to identify gaps and opportunities for improvement.

Risk assessment allows a firm to identify opportunities to implement controls that add value. During the course of an onsite inspection of a firm, FDA may note specific deficiencies to cGMP that ultimately end up cited and issued as Observations in a Form 483 or Warning Letter. The specific observation noted, in and of itself, may seemingly be small in scope. However, the specific matter cited is often representative of a much larger systemic gap or even deficiency at the Quality System level. FDA expects that organizations not only address specific observations cited in a Form 483 or Warning Letter, but are expecting to see a broader approach taken to identify the underlying deficiency at a systemic level, and implement one or more CAPAs to upgrade current good manufacturing practices to prevent reoccurrence. In addition, the agency is likely to expect that batches manufactured previously in that environment are properly evaluated under more stringent risk assessment and appropriate steps taken, if necessary, to adjust status of previous release criteria. This can result in a batch previously released being recalled or recategorized to rejection. Often the most effective way to go about such an endeavor is via formal risk assessment. Such an assessment will ultimately result in practices that are inherently designed to not only reduce the risk of occurrence (i.e. risk reduction) but also reduce the severity of harm (i.e. risk mitigation).

While regulations may not change drastically through the years, the way the industry approaches manufacturing – in terms of the quality system and the execution of the process and operation to the quality system – will regularly require change and evolution in order to remain current. A healthy quality system fosters current best practices through continuous improvement and preventative action initiatives. A regulatory agency, such as FDA, has the advantage of the collective insight across hundreds of global on-site inspections at organizations of all types and size. As a result, the agency is truly an authority on what is current best practice as a function of technological advancement and lessons learned. Firms should keep abreast of current regulatory thinking/focus by reviewing findings from recent inspections at other sites as well as by regular review of FDA news and events listed on FDA's website, [www.fda.gov](http://www.fda.gov).

## Governing remediation following a warning letter

The initial goal following a citation is to demonstrate to FDA that the ramifications of a warning letter and specific citations are thoroughly understood throughout the management of the organization to the CEO and evidenced by a collective effort to address and remediate these deficiencies. Contesting an observation or arguing a position is ill advised. A remediation plan should be managed collectively by a steering committee with primary ownership of the plan by someone with significant authority in the area of quality. To best meet overall objectives, the committee should be meeting frequently initially, several times per week, to assign and adjust scope of work and priorities, review progress and modify plans as needed. A critical early decision that needs to be addressed is related to the severity or totality of the observations and whether it is appropri-

ate to continue operating or voluntarily shut down during a period of the remediation. Such an evaluation is outside the scope of this article.

The primary roles of the steering committee should be to scope out the corrective action plan(s) and manage and assess impact to existing products previously manufactured in the facility undergoing remediation. As data is gathered and evaluated or re-evaluated, unforeseen issues or challenges may arise. There will be many decisions that need to be made during this process and a collective approach – represented and supported by quality and operations – needs to be ever-present to proceed down a path that holds true to initial objectives for remediation. It is important to note that as this path is explored and evaluated, often the scope of work in remediation may turn out to be much more extensive than originally envisaged.

It is critical that appropriate qualified subject matter experts (SMEs) are committee members and that these SMEs are meeting regularly to monitor the CAPA plans against the Warning Letter and ongoing operations, such as batch dispositions, shipments, and deviations. A number of industry experts are available on a consulting basis as SMEs, and many of these individuals formerly worked at FDA or may even be currently consulting with the agency on industry best practices. Unfortunately the cost of remediation can be extensive, both in terms of cash outlays as well as lost productivity due to facility downtime. But the true cost of remediation is a function of the time that a facility is not able to be productive and products are kept from the patient.

A risk managed approach should be used to identify the CAPA plans whereby the priorities for immediate risk assessment and CAPA implementation may be assigned. As assessments are conducted and information becomes available, a determination for appropriate or additional CAPA identification and implementation can be made. All determinations should be based on scientifically sound rationale with deference to current industry practices/standards. Hiring outside expert consultants is strongly advised.

Effective risk management for benchmarking current best practices to your operation requires a collective approach where multiple expert perspectives take part in the assessment. Optimally, it is a good idea to retain more than one outside expert consultant with the same or similar subject matter expertise to independently assess a single issue in order to gain an enhanced qualified perspective on best practice. Getting differing or even contradictory perspectives from outside consultants – which can easily occur – can be just as valuable as receiving unified perspectives, since both types will help to identify and arrive at what is best practice as well as what are the regulatory expectations. Ultimately, it is the firm that is the subject matter expert, not the outside consultant, on what control strategy will be best supported and practiced with the firm's facility, people, equipment, and quality system. The final decision needs to be supported by the totality of the science and risk assessments, which have been thoroughly evaluated and considered.

Remaining transparent with the FDA and demonstrating one's understanding of the observation(s), citation(s) and commitment to compliance should begin with the initial response, which is required within 15 days of receiving a Warning Letter. Once an observation is accurately interpreted and the deficiencies are accurately scoped out, the organization needs to assess what corrective action should be implemented in order to address the issue. However, if the scope may be considerable, it is not expected that within the first 15 days a

CAPA plan will be completely elucidated. Instead, the first response should be a description of the plan to evaluate and elucidate system deficiencies – i.e. gap analysis, risk assessment, etc. – to arrive at a detailed CAPA plan once the full scope of the observations or deficiencies are identified. This initial response should provide target dates for reaching certain key CAPA milestones (i.e. CAPA identification, CAPA plan for remediation, estimated overall CAPA completion), as well as a general timeframe for when a first update will be submitted to the agency. The initial response should also detail the plan; how the gaps will be, or have been, identified; and note that the organization will update the agency with specifics once the CAPAs have been completed. Note that the FDA may be receptive to an initial face to face discussion in the period immediately following receipt of a Warning Letter. Such a meeting can be useful in clarifying any question, and is a good vehicle to signal the firm's intent that this matter is being taken seriously and demonstrate a commitment to compliance. Attendance at such a meeting by a senior officer or company leader sends the right message to the FDA. As stated previously, any attempt to contest an observation or argue a position is ill advised.

Companies need to demonstrate to the agency that the observations cited as indicated in the initial response are understood and that a plan of action is or will be put in place to evaluate them. If this is not communicated, it could be cause for the agency to elevate the situation. For example, a Form 483 elevates to a Warning Letter and a Warning Letter elevates to a Consent Decree. Crafting an initial FDA response begins with an interpretation and follows with an appraisal of the corrective action(s). A collective effort is needed among SMEs in the organization together with key senior management to develop consensus as to forming an accurate interpretation of the observation(s) listed. It is critical that these efforts have the full backing and support of the CEO.

Just as it is important to demonstrate to FDA that the situation is well-understood and will be properly addressed and brought under control, the same is true with regard to communicating with employees and clients. For clients, it is important to keep the situation in perspective and demonstrate that CAPAs extend beyond the immediate observations to ensure public safety and secure a successful re-inspection. Keeping the process as transparent as possible for corrective action is recommended. In addition, many clients will first be interested in risk assessing products for quality impact you may have already manufactured and released to them before receipt of the Warning Letter. This may require considerable time and resource to manage in the early stages following the receipt of a Warning Letter, but is a critical process that must be completed. In addition, the FDA may be as or even more interested in this assessment than the client, because first and foremost is their focus on protecting the patient. With regard to employees, often the remediation process may involve process or SOP changes and more rigorous expectations and quality standards be put in place. It is important from the beginning of the remediation process to effectively and thoroughly communicate the organization's commitment to compliance and set the expectations that procedures, habits and operating behaviors may need to be improved. The more senior level leadership that plays a responsible role in setting the proper tone with the workforce ensures the odds for greatest success, particularly when in many circumstances organizational cultural changes may be required to complete remediation.

FDA citations may appear to be site specific, however, an organization needs to think holistically. Ultimately an organization needs to determine how the experience and lessons learned should be rolled out to other sites existing in the greater organization, if applicable.

## CMO specific challenges and opportunities

CMOs, by nature of their business, are exposed to a broad range of manufacturing demands and have an opportunity to develop a depth of knowledge to implement quality systems that are robust and flexible based on the nature of their operating environment. Corrective action is reactive in nature, so an organization needs to continuously look for opportunity to implement preventive actions as well, to ensure a *proactive* approach is taken to not just prevent recurrence but to prevent a problem from occurring in the first place. Best practices are constantly evolving and keeping current with industry practice keeps an organization at the leading edge.

Global CMOs that service a variety of technologies and products are subjected to varying global regulation. CMOs that are globally distributed are required to develop robust quality systems that standardize best practices to satisfy expectations across multiple regulatory agencies. Specific processes that a specialized CMO may develop and carry through to cGMP production may be executed in the early clinical stages whereby there are relatively few production runs executed over a long period of time, making it challenging to provide for on-the-job training and process familiarity on the manufacturing floor. Therefore, it is critical that the CMO have controls in place to ensure successful process execution by implementing an effective product specific training program, as well as standardizing practices for tech transfer and batch record authorship to ensure standard approaches for conducting common unit operations.

For CMOs that manufacture fill finished pharmaceutical products intended for parenteral use, sterility assurance is often considered the most critical quality attribute with regard to product quality and safety. The heightened criticality surrounding sterility assurance is a function of the limitations in testing coupled with the considerable amount of validation and qualification of the equipment used for component sterilization and/or supporting aseptic processing, as well as the people who must employ proper aseptic techniques at all times during operations involving aseptic processing. If a firm receives a regulatory citation for a deficiency in aseptic practices, it is important to take a holistic approach in risk-assessing one's entire sterility assurance program as it relates to the specific infraction and also the equipment, facility, personnel, and the quality system itself being used or implemented to support the sterility assurance program as a whole.

As regulations continue to evolve with progressing technology, manufacturers need to continue to challenge previously accepted practices to improve their quality systems and processes. Although navigating the regulatory landscape and remaining current can be challenging, opportunities to become a model for best practices in the area of manufacturing begins with an organization's own eagerness and investment in proactive risk management, which paves the way for risk-mitigating controls that can be considered feasible and valuable for one's operation.

### References:

1. Vesper, James L., *GMP in Practice, regulatory expectations for the pharmaceutical industry*, 4th Edition, 2011.
2. US FDA Guidance for Industry, Q9 Quality Risk Management, June 2006.

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