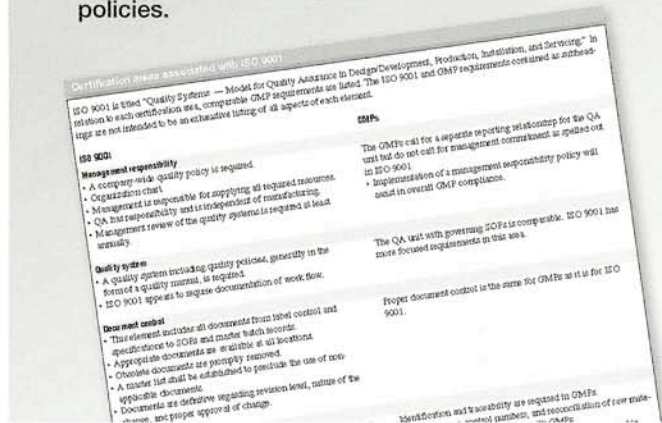


Quality Policies – Key to GMP Compliance

James E. Carter

This article explicitly advocates quality policies as a sound business practice and a way of increasing GMP compliance within the US pharmaceutical industry. Quality policies are executive management's commitment to and involvement in quality throughout the organization. They give employees clear signals as to expectations, and they provide guideposts and direction for the resolution of crises. The European GMPs and the US device GMPs strongly emphasize quality policies and the involvement of executive management. The US pharmaceutical industry could take a major step forward by instituting such policies.



James E. Carter, PhD, is principal of Omega Pharmaceutical Consulting, Inc., PO Box 3872, Gaithersburg, MD 20885-3872, tel. (301) 948-6106, fax (301) 840-8005, e-mail (carter@omegapharm.com).

Quality policies within the pharmaceutical industry are the key to compliance with current good manufacturing practices (GMPs). The ISO 9000 guidances require quality policies to ensure that executive management has established systems for quality. The European GMPs have been fashioned after the ISO 9000 guidances with emphasis on management's responsibility for quality. The US device GMPs have recently been revised, and they too require the establishment of quality policies by executive management.

Although currently the US pharmaceutical GMPs do not require the establishment of quality policies, their institution is sound business practice and is advocated in this article. Quality policies, like mission statements, define the basic values of the corporation for the myriad of decisions involving quality within the organization. Quality policies define numerous systems as well as executive management's commitment to quality. Through the institution of and adherence to quality policies, management obtains employee commitment to the quality system. Quality policies can assist all levels of management, especially executive management, in handling crises, and they ensure that quality has at least equal consideration with timing and cost. Quality policies become the basis for institution and evaluation of quality systems throughout the organization.

GMPs

The European GMPs were written with an emphasis on defining responsibilities. Chapter II, Article 6, titled "Quality Management," requires the manufacturer to establish a quality assurance (QA) system involving the active participation of management (1). The revised US device GMPs (issued 7 October 1996) place considerable emphasis on quality policies and quality systems (2). The quality system is defined in the device GMPs as "the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management" (3). The device GMPs state that "management with executive responsibility shall establish its policy and objectives for, and commitment to, quality" (4). These regulations are actually fashioned after the ISO 9000

series, which were first issued in 1987 and were most recently updated in 1994 (5). Each of these regulations or guidances advocates quality policies. Each emphasizes management responsibility and clear definitions of which organization or department will coordinate and have direct responsibility.

Chief operating officers and legal counsel within organizations generally have little knowledge of the Food, Drug, and Cosmetic Act, the *Code of Federal Regulations (CFR)*, or the reasons GMPs must be effectively implemented within their organizations. They may be unaware of the far-reaching effects of decisions within manufacturing, quality, product development, regulatory, and other departments within their organizations. Educating executive management regarding GMPs is the responsibility of the senior quality individual within the organization and may begin with the formulation and institution of quality policies. To FDA, ignorance of the law is not a legitimate defense, and executive management's involvement will be invoked with or without management's consent.

The US GMPs for the pharmaceutical industry do not explicitly require the involvement of "management with executive responsibility" and do not require quality policies. This article, however, explicitly advocates management responsibility for and involvement in the institution of quality policies for US pharmaceutical companies.

GENERAL PRINCIPLES FROM ISO 9000

As noted, the European GMPs and the US device GMPs have been fashioned after the ISO 9000 series standards. Thus, by reviewing briefly the principles and elements involved in the ISO 9000 quality requirements we can find the basic desirable principles that have been recognized by organizations with functions similar to those of the US pharmaceutical industry. This article is not advocating that companies become ISO certified; it is advocating that companies use sound principles in their business practices and that they gather sound principles from multiple sources.

The ISO 9000 guidance on quality systems is divided into five parts that are not specific for any industry but provide good business practices for development and manufacturing companies. ISO 9000 and 9004 are general guidelines. ISO 9003, 9002, and 9001 are quality systems for industries with varying degrees of complexity. ISO 9001 is the most complete model for QA systems and is titled "Quality Systems — Model for Quality Assurance in Design/Development, Production, Installation, and Servicing." The basic elements involved in the ISO 9001 quality systems are presented in the left-hand column of the sidebar, "Certification areas associated with ISO 9001." The right-hand column provides the current requirements of the US pharmaceutical GMPs for comparison with ISO 9001. Many elements in ISO 9001 have comparable requirements in the GMPs. Thus, document control, corrective action, quality records, internal quality audits, and training are common to both systems. Contract review and servicing are requirements of ISO 9001 that may not be applicable to pharmaceutical GMPs. Finally, some elements of ISO 9001 contain excellent quality principles, but they are not specifically covered by the GMPs — in particular, management responsibility and quality system. Institution of quality principles contained within ISO 9001 and other regulations can assist management within the pharmaceutical industry in complying with GMPs.

GENERAL GUIDANCE ON DOCUMENTATION

Before defining quality policies and their role in the pharmaceutical organization, it may be helpful to provide some principles for documentation in general. First is signatories: Every document needs to be signed and dated. The question then arises, Who should sign the document? Who is responsible? Which department is originating and using the document? Which departments are affected by the document? Who should review and approve it? In many organizations it is not uncommon for six to eight signatories to accompany every document. One person usually writes the document, and one or two individuals edit and ensure that the document is consistent with other documentation. Most organizations now require a QA approval signature. The regulatory implications of some documents have resulted in a regulatory approval signature on many documents. Although arguments can be made for many signatures, the questions listed above should be asked and signatories should be minimized. Too many signatories is one indication that the documentation system is out of control.

Standard operating procedures (SOPs) should stand alone and should not depend on other documents. Although this is a difficult principle to follow, it is highly advisable not to reference related documents within an SOP. Over time, documents are revised, obsoleted, or superseded. In many cases, references within related documents are no longer applicable and should be removed. Omitting references to related documents makes the SOP review cycle much more manageable.

Many documents have specific functions — for example, analytical procedures, validation protocols, and investigation reports of manufacturing deviations are common to all organizations. In each case, key sections of the document are examined for GMP compliance. The investigator is generally not qualified to comment on the mobile phase or the separation capacity of the chromatographic column. However, every investigator is very skilled at asking for system suitability requirements. It is advisable to format all analytical procedures in a similar manner and to have "system suitability" as a major heading for the analyst and investigator. Similarly, "acceptance criteria" in protocols and "corrective action" with manufacturing deviations can help the organization and the investigator ensure that conscious decisions have been made.

As one specific example, a company had received a rather lengthy deficiency letter from FDA and had employed legal counsel and consultants to assist with the responses. In many instances, the firm's response was to write another SOP. The company was already overpapered and was not following existing SOPs; adding another set of SOPs only added to the noncompliance and increased the bureaucracy within the organization. The company would have been better off had it instituted quality policies and quality systems and decreased the SOPs and the bureaucracy.

In summary, documents should be formatted with the same headings and in the same order. Keep documents simple, and avoid responding to inquiries or citations by writing yet another SOP. Good documentation makes it easy for responsible individuals to find needed information.

PURPOSE AND INTENT OF QUALITY POLICIES

Quality policies are defining, controlling documents that are put in place to assist executive management to be consistent in the

Certification areas associated with ISO 9001

ISO 9001 is titled "Quality Systems — Model for Quality Assurance in Design/Development, Production, Installation, and Servicing." In relation to each certification area, comparable GMP requirements are listed. The ISO 9001 and GMP requirements contained as subheadings are not intended to be an exhaustive listing of all aspects of each element.

ISO 9001

GMPs

Management responsibility

- A company-wide quality policy is required.
- Organization chart.
- Management is responsible for supplying all required resources.
- QA has responsibility and is independent of manufacturing.
- Management review of the quality systems is required at least annually.

The GMPs call for a separate reporting relationship for the QA unit but do not call for management commitment as spelled out in ISO 9001.

- Implementation of a management responsibility policy will assist in overall GMP compliance.

Quality system

- A quality system including quality policies, generally in the form of a quality manual, is required.
- ISO 9001 appears to require documentation of work flow.

The QA unit with governing SOPs is comparable. ISO 9001 has more focused requirements in this area.

Document control

- This element includes all documents from label control and specifications to SOPs and master batch records.
- Appropriate documents are available at all locations.
- Obsolete documents are promptly removed.
- A master list shall be established to preclude the use of non-applicable documents.
- Documents are definitive regarding revision level, nature of the change, and proper approval of change.

Proper document control is the same for GMPs as it is for ISO 9001.

Product identification and traceability

- This element includes rearward traceability (raw materials going into a product) and forward traceability (product being shipped to wholesalers and end users).

Identification and traceability are required in GMPs.

- Item numbers, control numbers, and reconciliation of raw materials are standard in complying with GMPs.
- Lot number/expiration dating and proper inventory and shipping records on product are required.

Inspection and test status

- Raw materials and product must be properly tagged at all stages.

Tagging and labeling of materials at all stages of receipt and production are part of GMPs.

Control of nonconforming product

- This element focuses on nonconforming product not reaching the customer.
- Corrective action, including removal of root causes, is part of this element.

Segregated quarantine, released, and rejected areas are part of the GMPs.

Corrective action

- This element includes investigating the cause, analyzing processes and information, initiating corrective action, applying controls to the corrective actions, and documenting changes resulting from the actions.
- Actions taken must be submitted to management for review.

Out-of-specification (OOS)/manufacturing deviations are part of the GMPs and are equivalent to the ISO 9001 requirements.

Quality records

- Quality records are used to verify that all quality systems (elements of ISO 9001) are being met.
- Procedures must be established for identification, collection, indexing, filing, storage, maintenance, and disposition of quality records.

A central documentation system that is properly staffed and capable of storage and retrieval of all records is standard in the GMPs and is equivalent to the ISO 9001 requirement.

Internal quality audits

- The program includes audits being scheduled during periods of activity and corrective actions that are documented.

Internal audits are part of the GMPs.

Certification areas associated with ISO 9001 — continued

Training

- A procedure is required for identifying training needs.
 - Training is a combination of education, training, and experience.
 - Training records are required.
- The requirements of this element are the same in the GMPs and ISO 9001.

Contract review

- This element is outside the manufacturing area and appears to be the responsibility of the sales department.
 - The act of selling is a contract and requires contract review.
- Not covered by GMPs.

Design control

- This element translates into product development and includes analytical and process validation.
 - Technology transfer is part of design control.
- GMPs look minimally into the R&D side of the organization but require validation.
- If production is relying heavily on R&D, GMP auditors may look for the technology transfer function.

Purchasing

- Work at subcontractors is covered by this element.
 - The element includes definition of requirements, selection of qualified suppliers, agreement on QA, agreement on verification methods, and provision for settlement of disputes.
 - Verification of purchased product does not absolve the subcontractor from responsibility.
- GMPs require qualification and control of subcontractors. The ISO 9001 requirements appear to be more definitive and complete than the GMP requirements.
- The elements listed in ISO 9001 are sound business practices.

Purchaser-supplied product

- This element requires procedures for verification, storage, and maintenance of purchaser-supplied product.
- Packaging and labeling that are purchased and incorporated with the product may be the GMP equivalent to this ISO 9001 element.
- Bulk product (e.g., bulk tablets) packaged and labeled for a second company may fall under this element.

Process control

- This element includes installation qualification (IQ), operational qualification (OQ), and process qualification (PQ).
 - Production processes should be verified as capable of producing product in accordance with specifications.
 - Documented work instructions are required. This translates into having master batch records.
- GMPs are comparable with ISO 9001 in this area.

Inspection and testing

- Raw materials and product must be tested and released at each step before moving to the next step.
- Raw material, in-process, and release-testing requirements are part of the GMPs and are comparable to the ISO 9001 requirements.

Inspection, measuring, and test equipment

- Equipment must be calibrated in accordance with its intended purpose.
- Calibration and maintenance of analytical and manufacturing equipment are required by GMPs and are comparable with the ISO 9001 requirements.

Handling, storage, packaging, and delivery

- This element ensures that good product will not be damaged by improper handling, storage, packaging, or shipping.
- This element is generally not part of a GMP audit.

Servicing

- Servicing is a contracted activity whereby installation or servicing of a delivered product is provided.
- Not applicable to pharmaceuticals.

Statistical techniques

- Statistical methods should be used to ensure control of production.
 - The statistical methods should be accurate and properly applied.
- The GMPs have comparable areas.
- Statistical sampling inspection of incoming goods is part of the GMPs.
 - The GMPs look for proper in-process controls.

Suggested titles for quality policies

Management Responsibility and Organization Policy	FDA Inspection Policy
Annual Quality Review Policy	Quality Policy
Audit Policy	Master Batch Records Policy
Bulk Pharmaceuticals Policy	Materials Control Policy
Change Control Policy	Recall Policy
Deviation Policy	SOP Policy
Equipment Calibration and Maintenance Policy	Training Policy
	Validation Policy

way it conducts business. In a crisis it is helpful to have agreed-upon guideposts in place. Quality policies help companies improve their internal compliance and total quality systems. By instituting and adhering to quality policies, management obtains employee commitment to the quality system.

Governing SOPs and GMP systems naturally flow from the policies. Once a policy has been defined, the governing SOPs and the specific SOPs that ensure proper execution of the policy can be readily defined. Like the mission statement, quality policies provide employees at all levels with values and information to consistently carry out their responsibilities. Suggested policy titles are contained in the sidebar above. The policies and titles as well as the responsible groups will vary from company to company but will undoubtedly have many common elements. The involvement of a company's executive management in formulating quality policies is vital. The chief operating officer within the organization should know what the commitments are within the Management Responsibility and Organization Policy and the Recall Policy. The legal and regulatory departments will want to concur with the FDA Inspection Policy. The formulation of individual quality policies should include the involved groups, depending on the placement of responsibilities within the individual organization.

In all cases the buy-in of all parties is vital to the success of the policy and the functioning of the system resulting from the policy. Playing politics, such as formulating a policy in the absence of a key player or with the intent to penalize a particular group or individual, will ultimately result in failure for the policy and the system.

FORMAT AND CONTENT OF QUALITY POLICIES

The format and content of the quality policies is also the responsibility of the individual company. Management or executive management will probably determine who writes and edits the individual quality policies. Some policies are undoubtedly the responsibility of executive management (e.g., the Management Organization and Responsibility Policy and the Recall Policy), but many can be handled primarily at the department level (e.g., the Change Control and Materials Control policies). However, as discussed in the General Guidance on Documentation section of this article, it is important to keep the policies simple and in the same format. Individual policies should be signed and dated and

Suggested common headings for individual policies

- Purpose
- Background
- Definition
- Policy
 - Responsibility
 - Resources
 - Organizational Structure
 - Management Review
 - Documentation of Review

should become part of the document control system. They may be prepared as a separate policy manual as suggested in the ISO 9000 guidelines. Policies should contain minimal information on specific procedures and detailed information regarding structure, responsibility, and review. The total number of pages for each policy should be kept to a minimum (one to three pages). Definitions within policies are important to ensure that all parties are speaking the same language and are starting with a common understanding. The policy should define the responsibilities of individual departments implementing the policy and should ensure that adequate resources and structure exist for successful implementation. Finally, each policy should be reviewed annually to ensure that it is current and applicable in a changing environment. A suggested format for each quality policy is contained in the sidebar, "Suggested common headings for individual policies." The main headings of purpose, background, definition, and policy should be constant, but the subheadings in each policy will vary.

CONCLUSIONS

Quality policies are good business practice and are key to GMP compliance. Properly written policies provide the values and framework within which members of the organization can behave consistently. Defining responsibilities before a crisis ensures that a system is in place to handle the crisis and that the organization is able to weather the storm. The European GMPs and the US device GMPs have followed the ISO 9000 series in defining quality requirements for responsibility and structure. This article uniquely advocates quality policies and quality systems for the US pharmaceutical industry. GMPs have always emphasized the word *current* to allow FDA to move the industry forward. However, the industry can move itself forward without FDA's prompting by implementing quality policies.

REFERENCES

1. European Community Directives — Directive 91/356/EEC, 13 June 1991.
2. *Code of Federal Regulations, Title 21, Food and Drugs* (General Services Administration, Washington, DC, April 1998), Part 820.
3. *Code of Federal Regulations, Title 21, Food and Drugs* (General Services Administration, Washington, DC, April 1998), Part 820.3.
4. *Code of Federal Regulations, Title 21, Food and Drugs* (General Services Administration, Washington, DC, April 1998), Part 820.20(a).
5. American Society for Quality Control — ANSI/ISO/ASQC Q9001-1994. ☐