

Focus On Compliance

So What Are GMPs, Anyway?

by James L. Vesper

People entering or becoming familiar with the pharmaceutical industry, including the production of drugs and vaccines through biotechnology, quickly encounter a set of regulatory requirements known as "Good Manufacturing Practices" (GMPs). For companies, following GMPs is essential to getting new products approved by regulatory agencies and for producing drug products that have the required safety, identity, strength (or potency), purity, and quality. For individuals — at all levels — adhering to GMP requirements and principles is critical so that every action and decision contributes to products that meet the expectations of patients, healthcare professionals, and regulatory agencies.

So just what are GMPs anyway? They are the requirements that manufacturers of regulated health-care products must follow so that the products they make have the safety, identity, strength (or potency), purity, and quality that they purport or are represented to have. Expanding upon the definition gives us a richer understanding.

GMPs are the requirements . . . In most countries, GMPs have a legal aspect: They can be part of a nation's food and drug law (as they are in Canada) or regulations that have been issued by a regulatory agency (as in the United States). These requirements are enforced by regulatory officials who evaluate compliance through on-site inspections, review of documents, and random testing of products. For example, the Canadian Health Products and Food Branch Inspectorate (HPFBI), Britain's Medicines Control Agency (MCA), and the US Food and Drug Administration (FDA) conduct inspections of manufacturing companies in their respective countries and in most cases, companies in other countries that export into their countries.

One aspect of GMP that is different from other types of regulation is that not all the requirements that need to be followed are clearly written in the regulations or in supplemental guidance documents that regulatory agencies frequently issue. The FDA expects many things that aren't specifically stated in its regulations. The FDA does state, however, that its "Current Good Manufacturing Practices" or cGMPs (sometimes written CGMP) are the "minimum requirements" (1), and that what defines a manufacturing practice as current and good is being "feasible and valuable in assuring drug quality"(2). In other words, the FDA expects companies to use the systems and practices that provide the best control over a process or product or information used to make a decision about a process or product. These evolving expectations make understanding and implementing GMPs a dynamic activity that needs continual review.

That manufacturers . . . Anyone involved in pharmaceutical production — including the production of clinical trial materials — is subject to GMPs. The US FDA defines covered groups as those working in "manufacture, processing, packing, holding, including packaging and labeling operations, testing, and quality control"(1). The Canadian GMPs apply to the "fabrication, packaging, labeling, distribution, testing, and wholesaling" of drugs (3). For companies that use contractors for manufacturing or testing, GMPs apply to both the contractor and, ultimately, the company that has its name on the label.

Of regulated healthcare products must follow . . . The specific products that must be manufactured under GMP vary, but most countries include at least prescription and over-the-counter medicines, blood and blood-derived products, vaccines, antitoxins, and active pharmaceutical ingredients that are marketed, sold, or distributed.

Have the safety, identity, strength, purity, and quality . . . These are the characteristics (SISPQ) of a GMP-compliant product:

Safety. The product is free from unknown side effects when used as directed. *Identity.* The product is what the label and labeling describe it to be. All personnel, equipment, actions, and decisions involved in its production are identified and documented so that the process can be reconstructed from the records.

Strength (or potency). The product delivers what its label claims throughout the product's shelf life.

Purity. The product is free from microbial, chemical, and physical contamination.

Quality. The product meets regulatory requirements wherever it is sold, and it can be made consistently, time after time.

If a product does not possess the above characteristics or is not produced or tested according to GMP, the product is considered adulterated and not fit for use.

EVOLUTION OF TODAY'S GMPs

GMPs didn't occur overnight or simply appear as regulatory requirements. They are based on quality principles and business practices that have evolved over time. From the 1900s to the 1950s, the quality of a product was determined mainly by testing it to determine whether it met specifications. No one was really sure that something was acceptable until all the test results came in. From the 1950s to the 1970s, quality gurus like Edward Deming and Joseph M. Juran (whose work was initially ignored in their native United States) were convinced that industries could save money and materials if companies used practices such as statistical process control and continual improvement. The idea of building quality into the product began to take hold. This expanded to designing quality in from the very beginning, so processes could produce products that met the predetermined needs of customers. GMPs were formalized in the 1960s and 1970s with this philosophy in mind.

Learn from the Good. GMPs also arose from best-of-industry practices. For example, in 1884, one manufacturer (still a major company today) stated in its price list that "each lot of drug is EXAMINED BY ASSAY before manufacture. We make no extra charge on this account as we consider it our highest duty to know our preparations to be of uniform and full strength" [all emphasis in original] (4). It also tested raw materials (botanicals like roots and bark) when they arrived so that the company could be assured it was getting what it paid for. Final product and incoming testing are now standard elements of GMP systems.

In the United States, an "Inspection Manual" of May 1945 listed items that agency inspectors should examine when they conducted comprehensive drug inspections. The list included records, tests, and adequacy of facilities and equipment. This guideline was expanded in 1955 to more than 10 pages with details of the methods and controls that were to be examined. Many things listed in the 1955 guide are found in GMPs today.

The industry was also trying to set standards for manufacturing control during that period. The Pharmaceutical Manufacturer's Association (now the Pharmaceutical Research and Manufacturers Association, PhRMA) published a document in 1961, "General Principles of Quality in the Drug Industry," that established guidelines for the industry. This document included many of the items found in the FDA's inspection manuals; later cGMP regulations also parallel this industry document.

Learn from the Bad. Contrasted to those best practices were bad practices, some of which were highlighted in 1962 US Senate hearings examining the poor manufacturing practices found at some companies. Lack of training and inadequate manufacturing facilities, equipment, and process controls were mentioned. One speaker (the Secretary of Health, Education, and Welfare) contrasted the mandated regulation and training of pharmacists with the lack of regulation and training of those making and testing drugs (5).

Tragedies that showed the critical need for practices to ensure that products had the five GMP characteristics of SISPO were another force that shaped GMPs over the years. In England, while a draft was being circulated in 1972 of what would become the British GMPs (*Rules and Guidance for Pharmaceutical Manufacturers and Distributors*, still known as the "Orange Book" because of the color of its cover), five people died as the result of microbially contaminated intravenous fluids. The government study on the

incident, known as the Clothier Report, found that a combination of “simple carelessness [and] poor management” contributed to the tragedy (6). In the United States in the mid-1970s, a similar problem with intravenous bottles that were contaminated after being terminally sterilized was the impetus for aseptic processing validation.

The ICH Q7A GMP requirements for active pharmaceutical ingredients include the need to identify clearly the producer of a product, in part because of the deaths of nearly 100 children in Haiti in 1996 due to a contaminated solvent, the specific origin of which was in question. GMP requirements are reactions to prevent industry problems from happening again. We need to learn from the past in order not to repeat its tragedies.

ESSENTIALS OF GMP

It is useful to read through the GMPs of different countries (or regions) to see how they approach creating products that have SISPO. The Canadian (3) and European (7) GMPs and the ICH Q7A (8) GMPs are much more similar to each other than they are to the US cGMPs (1). The Canadian, EU, and ICH documents also have an important opening section on quality management and its role in creating GMP-compliant products.

Similarities among the requirements are much stronger than the differences. The essence of GMP can be summarized into seven elements:

1. Protect the product from contamination.
2. Prevent mix-ups.
3. Know what you are to do before you do it.
4. Document what really occurred.
5. Strive for consistency and control.
6. Have an independent group make the final decisions.
7. Solve problems, learn from mistakes, monitor, and continually improve.

Expanding these essentials and what they involve allows us to see some of the well-recognized concepts of GMP.

Protect the product from contamination. Of the seven essentials, this is the most critical. A product that contains unwanted cross contamination (from other products), microbes (molds or bacteria), particulates (metal shavings or dirt), physical objects (bolts or pens), or other chemicals (sanitizing agents or pesticides) can cause serious or fatal injuries.

Prevent mix-ups. Ensuring that the drug product, the label, and labeling are all in agreement is only part of this essential. All raw materials, intermediates, equipment, and processing steps must be identified so that one can immediately determine anything’s identity and status. Examples of status include clean or dirty (for equipment or facilities) and approved, quarantined, rejected, or released (for materials or products).

Know what to do before you do it. Documentation systems are used to produce and control functional documents that tell how to do something (master formulae, procedures, methods, protocols) or help in making decisions (specifications). Reviews and approvals by subject-matter experts, management, and the quality unit help ensure that the content is correct and complete. Training — on the procedures, processes, and in GMPs — enables people at all levels to perform their responsibilities consistent with GMP expectations.

Document what really occurred. Carefully prepared records allow for a rapid and reliable re-creation of an event, action, or decision. Recordkeeping standards and practices need to ensure that the records are complete, permanent, and accurate. If electronic records and signatures are used to meet GMP requirements, they must be created and stored so they are reliable and trustworthy. Record retention systems ensure that documents and records are readily available to those who need them, including regulatory inspectors. (Batch manufacturing records are a hybrid: They tell what to do and also are used to collect information about how the batch was actually made.)

Strive for consistency and control. This requirement is achieved in three phases. First, define what is to be controlled: Identify critical processing parameters, specifications, and functional requirements. Next, demonstrate that adequate control can be achieved through installation qualification, operation qualification, performance qualification, and process validation. Finally, use calibration, preventive maintenance, and change control systems to maintain control. Change control ensures that the approved characteristics of the drug are maintained. More simply, it helps prevent unwanted surprises. Change control is the most complicated element in a pharmaceutical or biotech company's quality system.

Have an independent group make the final decisions. A philosophy that runs throughout GMP is the role of the quality control unit (also referred to as quality assurance or simply as "quality"). This doesn't mean that it is solely responsible for producing high-quality products; every group has a role to play. Instead, the quality control unit must be given the authority and responsibility to do its job effectively. The quality control unit must also approve procedures, specifications, and protocols that are used in GMP areas. The unit conducts internal quality and compliance audits and certifies vendors and third-party contractors. Although the quality control unit can delegate some of its responsibilities (analytical testing on incoming materials and finished products, for example) it must make often difficult decisions about approving or rejecting materials and final products.

Solve problems, learn from mistakes, monitor, and continually improve. All quality systems — ISO 9000, Total Quality Management, Six Sigma, GMP — have a common component: They include ways to continually improve. Monitoring products and processes gives assurance that all is well — or can give early warnings of potential problems. Looking broadly at the pharmaceutical industry and companies both large and small, this is the element that is most in need of strengthening.

We can now see how the seven essentials of GMPs and SISQP are related: To create products that have the GMP characteristics of safety, identity, strength, purity, and quality, companies and individuals need to fully adopt the seven essentials of GMP. Each company defines how it accomplishes the essentials for its particular products and in its unique circumstances through policies and procedures.

Establishing a GMP system in a pharmaceutical company takes time and resources. Making sure every action and decision is consistent with GMP takes the continual, enthusiastic dedication of everyone within the company, even when it takes a little longer or when shortcuts are appealing. We have GMPs for regulatory and legal reasons, but their real importance is in protecting the health and confidence of those using the products we help make.

REFERENCES

- 1 Food and Drugs Scope. Code of Federal Regulations, Part 210.1a, Title 21, www.fda.gov/cder/dmpq/cgmpregs.htm.
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- 3 Available at www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/guidmain.html#GMP.
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- 5 House Committee on Interstate and Foreign Commerce, 87th Congress, 2nd Session, pp 62–63.
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- 8 Available at www.ich.org/pdfich/Q7Astep4.pdf.

James L. Vesper is president of LearningPlus (www.learningplus.com), Rochester, NY, and executive producer of pharma programs for LearnWright (www.learnwright.com). In both organizations, he uses his 22 years in the pharmaceutical industry in developing and presenting GMP-related training programs for pharmaceutical and biotech companies in North America, Europe, and Asia. He can be reached at jvesper@learningplus.com or 585-442-0170.