Some Thoughts on Current Good Manufacturing Practices

By Robert Schiff, PhD, RAC, CQA

In writing this article, rather than discussing GMPs as they appear in the Code of Federal Regulations and guidelines, I decided to present some thoughts on the GMPs from the perspective of 36 years in industry.

Good Manufacturing Practice for drugs is traditionally believed to have started with the 1938 regulations describing the *Federal Food, Drug and Cosmetic Act* (*FD&C Act*).[1] This act was a response to more than 100 deaths from an elixir given to children and babies that was thought to be made with a safe glycol. In fact, it was manufactured with diethylene glycol, or antifreeze.

GMP History

Many of us trained in this history know that the manufacturer, Massengill (now a subsidiary of GlaxoSmithKline), never expressed regret or apologized. As a result, Congress, which is generally reactive and not proactive, enacted legislation that gave us the current practice of controlling manufacturing.

This is not to say that GMPs began with the *FD&C Act*. FDA, in a recent publication celebrating its centennial, indicated that products, at least food, were regulated during the time of the colonists.[1] For example, in 1641, the Massachusetts Bay Colony required the inspection of pork, beef and fish for adulteration. Also in the 1600s, Virginia had laws that stopped the sale of adulterated wines.

In the early 1900s, with the serialization of Upton Sinclair's *The Jungle* and Teddy Roosevelt's investigation of the Chicago slaughterhouses, food processing was in the limelight. This resulted in food GMPs. Drug controls took a later path. Although Kallet and Schlink, in their classic *100,000,000 Guinea Pigs,* written in 1933, recognized the dangers of bad drugs,[2] it was not until the Massengill fiasco that Congress passed the *FD&C Act* of 1938. This added safety and tolerance requirements in manufacturing where poisonous substances were concerned and authorized factory inspections.

This brings us to what is meant by "current" Good Manufacturing Practices. This term refers to the state of the art at a given time. At the time of the Massengill incident, GMP apparently did not include performing quality control checks on raw materials, in-process goods and finished products. So, was the company compliant with industry standards at that time? Difficult as it may be to believe, it probably was. But, as things turned out, cGMP was not enough to ensure safety. Thus, there was a need for formal guidelines and regulations.

For the past 70 years, regulated product manufacturing has improved because of controls implemented to ensure safety and efficacy. FDA has promulgated regulations and guidelines controlling food (21 CFR 110[3]), dietary supplements (21 CFR 111[4]), drugs (21 CFR 210[5] and 211[6]), biologics (21 CFR 600[7]), devices (21 CFR 820[8]) and tissues (21 CFR 1271[9]). What, then, is the common feature among these regulations?

Controlling and checking raw materials, in process goods and finished products is the common thread winding through reviewed and completed documentation. Arbitrarily changing processes and specifications is frowned upon and many changes, even today, require FDA approval.

There are, of course, variations in the degree of testing and confirming raw materials. For example, for drugs, the regulations under 21 CFR Part 211 require that all raw materials be tested or that the suppliers meet GMPs established through audit or material testing. Device regulations under 21 CFR 820 do not require the same level of testing of critical components. However, the finished goods manufacturer must verify or ensure that the critical component does what it is supposed to do. It is not clear why FDA does not require the establishment of specifications and testing for these components.

Guidelines for one area of raw material testing involving Quality Control (QC) do not seem clear. Under the Code of Federal Regulations Part 211, as stated above, manufacturers need to control their raw materials for production. If the manufacturer tests the "raws" to identify nonactive ingredients and assays the actives, does it also have to test the raw materials that go into QC reagents? When the question arose several years ago, I contacted CDER twice and never received a response.

I had an opinion on the subject but because I did not get a response from CDER, I contacted the New Jersey and Dallas FDA District Offices. The compliance officers are no longer with the agency, but the Dallas officer said no and the New Jersey officer said yes.

As an auditor, I routinely check Quality Control records that are part of the batch record. In my experience, larger companies test the raw materials that go into QC reagents. Some small companies do and some do not. In my audits I follow the dictum that the Quality Control function needs to be as transparent as possible since QC performs the product's pass/fail function. If QC's raw materials are not tested, it is being held to a lesser standard than other areas whose materials it tests. The recommendation I follow is that of the New Jersey District Office's compliance officer. (Please feel free to offer your comments and opinions on this question in Letters to the Editor or to my email at RSchiff13@aol.com.)

PDR and DHF

The next items for discussion are the Product Development Report (PDR) for drugs and the Design History File (DHF) required for devices under 21 CFR 820.30.[10] Each of these could be an article in itself. A discussion and a little history of each follow. Both are GMP functions because they explain the origin of process and quality control, although somewhat differently.

In the past, when a New Drug Application (NDA) was submitted to FDA, the PDR, which was the history of the process and specifications, had to be available during the Preapproval Inspection (PAI). Today, the NDA's Common Technical Document (CTD) format requires that a Pharmaceutical Development Report be included. This is essentially the old PDR.

The DHF can be considered the device equivalent of the PDR although the former's derivation is quite different. Several years ago, a number of devices were recalled. FDA asked one of its CDER staff, Dr. Robert Temple, to study and report on the problem.[11] This led to the guidance document, *Design Control Guidance for Medical Device Manufacturers*.[12] I will not go into detail on the motivations and arguments against the conclusion; those can be left for another review. However, to paraphrase, the report concluded that the recalls were due to design flaws by the manufacturers. As a result, design control requirements were elucidated and the Design History File came into being. Unlike the PDR, the DHF requires formal reviews after various development stages (input, output,

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transfer, etc.). The requirement was codified as 21 CFR 820.30.[10]

The DHF, although new to the US, was already a requirement in Europe. To obtain a CE Mark and enter the EU marketplace, certain devices had to comply with the *Medical Devices Directive* (*MDD*),[13,14] which required, among other things, the DHF.

When 820.30 was promulgated in the *Federal Register*, manufacturers were given ample time to meet the requirements for postpublication implementation. However, what appeared to be overlooked was how to create a DHF for in vitro diagnostic (IVD) products. While IVDs lend themselves to DHFs in some ways, the formal reviews required in 820.30 appeared to be extra work that added time and effort to development. It was suggested that 820.30 be amended to recognize differences between diagnostics and device equipment but little has been done to change the regulations. The EU, however, has implemented the *In Vitro Diagnostic Devices Directive*.

GMPs Today

The last items I wish to discuss are some actions FDA has taken to "improve" GMPs and, thereby, product quality. Legislation and regulations requiring controls for manufacturing give rise to uniformity of product within certain limits of variation.

FDA published *Quality Systems Approach to Pharmaceutical CGMP Regulations* in September 2006.[15] It is similar to the Quality Systems Regulation for devices and emphasizes quality by design in product development and risk management. According to the guidance, "Quality by design means designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process." Maybe I misunderstand this FDA initiative, but isn't this what manufacturers do already?

One item, "Quality Risk Management," is an outgrowth of the ICH guidance on risk (Q9) and is new in this FDA guidance. Starting risk management early in the development process increases quality by reducing error. The structure of risk analysis and risk management has been discussed in a variety of documents and will not be elaborated on here.

The remainder of the guidance deals with FDA's systematic approach to inspection. It defines the methodology FDA uses to conduct its inspections. This leaves the questions of whether this approach (i.e., systems) is anything more than an FDA tool to utilize its resources more efficiently, and if it will, in fact, improve quality.

As this article goes to print, recent headlines and congressional investigations have criticized FDA for such compliance issues as failing to inspect raw materials manufacturers in other countries. Concerns about the review of clinical information arising from the Vioxx and Avandia incidents have added to the cacophony of criticism of the agency. One can only guess what the outcome will be. However, it seems almost certain that FDA will increase in size and that the regulatory burden on industry to meet GMPs probably will increase as well.

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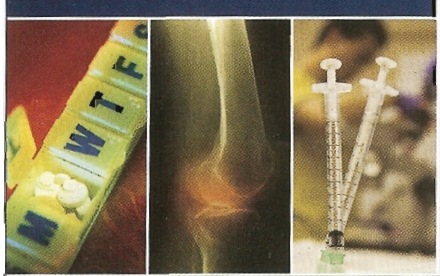

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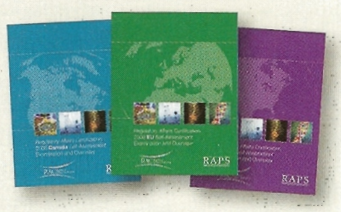

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