

Docket Number 03N-0059

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Janet Woodcock, MD
Director
Center for Drug Evaluation and Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Woodcock,

I wanted to take a moment of your busy schedule to provide some suggestions into the cGMP Implementation project that is being undertaken as part of the Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century initiative.

Since October 2000 I have been an independent consultant – after 24 years with FDA. Since 1976 I have been involved in compliance, inspections and enforcement, first as a regulator and now as a consultant. I have first hand knowledge of both agency policy and procedures and industry practices.

At FDA as the team leader for the Quality System Inspection Technique (QSIT) project from 1998 to 2000 I was responsible for drafting proposals, the open public meeting, numerous federal register announcements, the writing of both QSIT and the implementing compliance program – as well as training for all the device investigators and district compliance officers. I worked in concert with ORA, OCC, the Device Field Committee, the investigators and compliance officer (users) and industry. I even faced the employee union when addressing concerns about QSIT implementation. I certainly could talk about the bumpy road we took to change a major inspection and enforcement program.

Since leaving FDA I have been working with both pharmaceutical and device companies – but mostly pharmaceutical companies. What I am finding is a hunger for knowledge about quality systems as well as a fairly consistent lack of implementation of quality systems in the industry. The 1978 Drug GMPs are simply antiquated. The bar has been raised as evidenced by inspections and even the CDER compliance program – where mention is made of a Quality System. It is glaringly obvious that the 1978 rule does not mention the words “quality system” and yet FDA has an expectation that industry have one. This is where I come in to advise and teach about quality systems.

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I urge CDER to look at the Medical Device Quality System Regulation as a model when developing the new drug GMP. The beauty of the Medical Device Quality System Regulation – which was harmonized with the 1994 ISO 9001 standard - is that it is preventive. If followed, the companies are more likely to not have major problems. The preventive areas are Design Control, Corrective and Preventive Actions (CAPA), Validation (production control), Management Review, Audits and of course some basic preventive programs such as document control and calibration and maintenance. Yet when I visit pharmaceutical companies I often find lack of CAPA programs, no management review, and a poor audit program.

Sadly, many companies don't have these programs because they are not required. I also find problems in maintenance and calibration programs and major holes in validation programs. I'm sure you know the investigators find the same things in plant inspections. The reality is that the pharmaceutical industry needs all those programs (I call them "systems") to make pharmaceuticals in a manner that will assure consistent and quality results. I believe that having those systems in place will also result in less recalls, less investigations, less product loss and more profits for the industry.

An important yet often misunderstood (or utilized by FDA) aspect of the Quality System Regulation is the emphasis on management. In fact, when I was teaching QSIT to the field and industry I often cited management as the key ingredient in a quality system. The way it works is as follows: Management with Executive Responsibility is defined in the regulation – and a Management Representative is required. During the inspection the agency determines whether an adequate quality system is established and maintained at the facility. If it is not, then the 483 can cite Management with Executive Responsibility for failing to do his or her job. This is a big issue because most 483s cite a process, document or piece of equipment – not a person. I believe that if we can hold management responsible (the FD & C Act already does so) via regulation we have a greater chance of making them do their job.

Too often high level executives at drug companies don't have time to listen or be involved in quality system issues. There is no requirement for them to do so. However under the FD & C Act (using the Park decision as precedent) they are responsible for the company's GMPs and quality system. Often this Aha experience does not happen until a warning letter comes in the mail addressed to them. My experience is that those top executives often rose to their positions from the ranks of marketing or finance. Those top executives rarely if ever arise from the ranks of manufacturing or quality. We need them to be involved sooner. It may take some lines in a GMPs regulation to do so. The quality system must be on the radar screen of the top executives just as sales and marketing data is on their radar screen every day. They must know about (quality system) problems and be involved in fixing them. I believe one reason the state of GMP

compliance in the drug industry is lower than it should be because of lack of involvement of top executives.

Will management controls by itself increase the compliance of the pharmaceutical industry? I believe not. The management controls must be supported by a strong audit and CAPA program to assure problems are weeded out and acted upon. It is the management review process that sits the executives at the table to review data from CAPA and audits. It requires them to review the data and make improvements to the systems.

Reading the Schering Plough consent decree you find a section on Management Controls (interesting since the drug GMP does not mention that section). This section tells the company to appoint an executive to watch and stay on top of all quality system issues and report regularly to the very top of the company on progress or lack thereof. Obviously CDER must have recognized the importance of management controls to have put this in the consent decree. I believe we need management controls in the drug GMP, not just in consent decrees.

Before I leave this topic I want to mention that I strongly believe that if companies had strong management controls we would have less need for inspections. It should not be the responsibility of the field investigators to find every quality system problem at every company. It is the responsibility of the executives of those companies to weed out and correct problems. We could save many field resources if we could make the executives FDA surrogates, more or less. And make them responsible to do their job of assuring the systems are in place and operating adequately. The job of the investigator should be to go in a company and take a snapshot of their systems and processes – not to look under every rock and find every problem. Companies must be the ones looking under every rock – if they need third parties to look under those rocks, that's OK too. But the companies should be the ones finding and correcting quality system problems. FDA can not physically – nor should they be the ones to find and documenting each and every problem at the companies. If the snapshot inspection finds lack of adequate systems use the agency's enforcement tools to achieve corrective actions. But place the burden where it belongs.

Finally, you may know the industry throws away a huge amount of product because it does not meet specification. (I am certain it is many \$ millions – possibly hundreds of \$ millions) It is my belief that this loss could be greatly reduced if the companies implemented quality systems. Sadly I believe that many people in the industry do not appreciate the benefits of quality systems. I had the experience of discussing ISO 9001 with a company president. He said he thought it would not benefit his company. Like many in the industry the lack of appreciation for the standard is common. But it is not the ISO standard itself or the certificate in the lobby that makes a quality system – it is the intent and desire of company representatives to assure systems are in place and assurances that they operate adequately. I urge you to look at the ISO 9000-2000 standards

when revising the drug GMP. Also look at the medical device program. They are good benchmarks. You should obtain feedback from FDA and industry experts.

I am sending this letter for two reasons. First, I think it is important that you understand and appreciate the benefits of moving in the quality system (i.e. the ISO 9000:2000) direction when revising the drug GMP. Second I wanted you to consider contacting me about sharing my experiences and knowledge of quality systems as you move further into the initiative. I would be happy to visit CDER to discuss my thoughts, experiences and opinions.

If you wish to discuss any of this further, please have someone on your staff contact me. I am sending copies of this letter to docket management for discussion at the April 22-24 GMP Workshop, and Commissioner McClellan.

Sincerely, 

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CC: Mark B. McClellan, M.D., Ph.D., FDA Commissioner
✓ CC: FDA Dockets - HFA-305 (Docket Number 03N-0059)