

Docket No. 2004D-0443

November 29, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Dear FDA,

This document provides comments and suggestions on the September 29, 2004 FDA document entitled the Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. The document was published by FDA as part of the “Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP) for the 21st Century initiative”.

I have been involved in compliance, inspections and enforcement from both the agency side and the industry side.

- I worked for FDA for 24 years – between 1976 and 2000. My FDA experience started as a field investigator (doing drug inspections in the Chicago District). My ending FDA position was a branch chief in the CDRH Office of Compliance in Rockville, MD. Also at FDA I was the team leader for the Quality System Inspection Technique (QSIT) project.
- Since October 2000 I have been an independent consultant. My client base is pharmaceutical, bio-pharmaceutical and medical device companies.
- My specialty is Quality Systems and Good Manufacturing Practices.

At the outset I commend FDA and CDER for issuing the Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. The document fills a void that has existed in the industry for a long time. It puts the industry on notice that the Drug GMPs alone can not provide adequate guidance for producing pharmaceuticals in the 21st century. The world of quality has evolved greatly since 1976. It is time the FDA acknowledges it to the pharmaceutical industry.

That being said I am providing comments on two distinct topics:

- The process being followed by FDA and CDER to upgrade the industry's quality systems, and
- The Guidance Document itself.

The Process Followed by FDA

My initial comments are about the process being followed by FDA and CDER to establish the quality system requirements. I am disappointed that FDA could not replace the old 1976 Drug GMP with a new Quality System based GMP Regulation (21CFR 211). FDA and CDER took the easy way out and published a "Guidance".

The new FDA guidance is, in your words, "approximately organized according to the System Based Inspection Program". Yet the System Based Inspection Program is an internal FDA Compliance Program – a document designed for FDA compliance officers and field offices. Basing an industry guideline on a compliance program is backwards. The normal FDA rulemaking process (like the one used by CDRH) would be as follows;

- 1) Get industry and FDA to agree on a new Drug GMP regulation based on a quality system framework - harmonizing to an international standard such as ISO.
- 2) Publish the GMP regulation in the Federal Register for comments, and eventually in the Code of Federal Regulations (21CFR 211).
- 3) Develop a tool for the field investigators to use for evaluating the industry's' compliance to the new GMP regulation (such as the QSIT Guide)
- 4) Publish a Compliance Program for the FDA to use for providing guidance to FDA field and center staffs for the inspections and administrative/enforcement activities related to the Good Manufacturing Practices (GMP) regulation.

I am aware of the time and resources it would take to publish a new drug GMP. Additionally, politics plays into the equation when FDA attempts to impose a new regulation on industry (as opposed to a guideline). I believe the time and effort are worth spending. The pharmaceutical industry needs a strong and lasting GMP that will serve to protect the public and assure drug products are made to the highest standards – with active involvement of a quality system in place at the companies.

The right thing to do is publish a new GMP in the code of federal regulations which will make them legally enforceable in administrative and legal proceedings. It appears that FDA and CDER chose to go the fast route and shortcut the process by going the guideline route to achieve the same (attempted) goal. I am worried the goal will not be achieved. Court challenges to FDA enforcement actions based on the "Guideline" are inevitable. They will be costly (as FDA knows from previous court actions based on enforcement of Guidelines) and may actually set the FDA back in the long run. Short term gains may be made but long term enforcement will be lost.

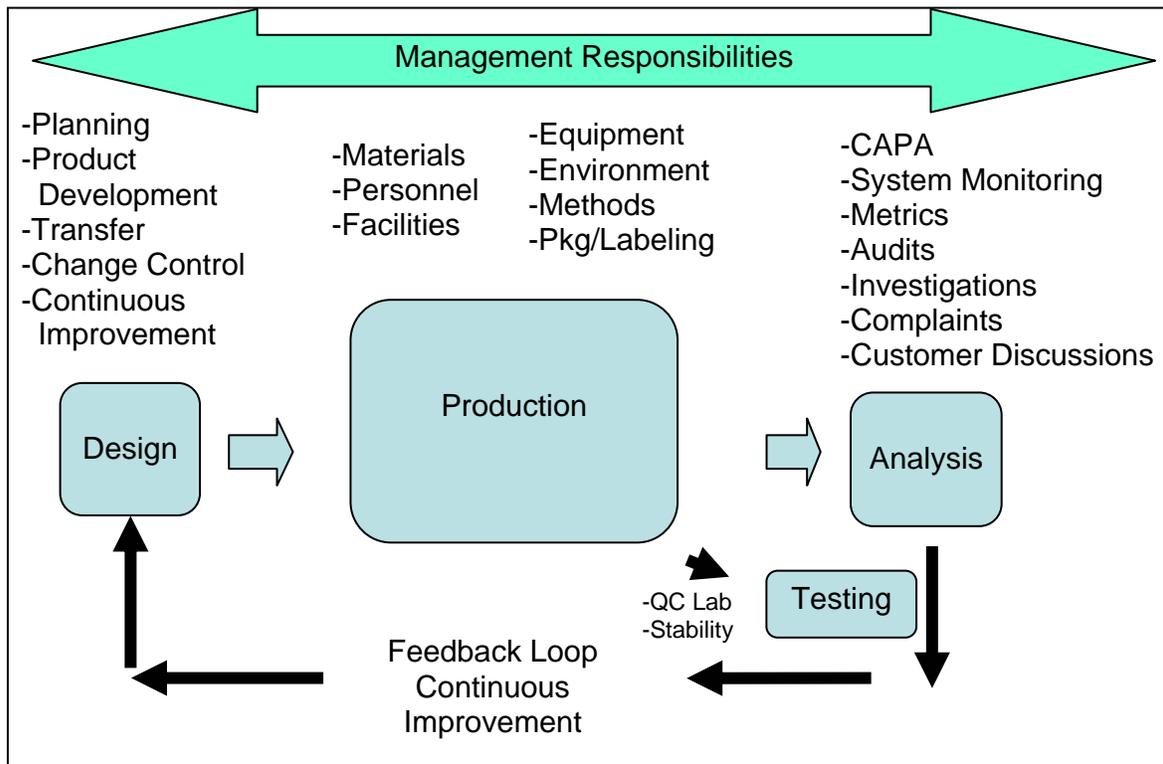
In the guidance FDA acknowledges that "The cGMP regulations do not specifically cover these additional quality elements." It further states "FDA's

guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.” Since tables are provided in the guidance document listing “Quality System Elements” and “Regulatory Citations” it appears the FDA is justifying the new quality system elements as requirements. Review of the tables, however, finds they do not coincide with 21CFR 211 sections as stated, unless one were to make a liberal interpretation of the CFR. Surely this is a loose way to regulate the industry as opposed to the straightforward rulemaking method described earlier.

Comments on the Guidance

Six-System Diagram versus Closed Loop Systems

I am disappointed by FDA’s insertion of the drawing entitled “FIG. 1 - SIX-SYSTEM INSPECTION APPROACH”. This drawing only solidifies my previous comments that the guidance is based on an inspection tool (the compliance program). The six elements listed are elements needed for product realization – they are not quality system elements. What is needed is a drawing showing where and how quality system elements should be utilized by the industry. My version of the appropriate drawing:



Drawing by Timothy Wells, QualityHub, Inc.

Review of the FDA drawing shows it falls short of the understanding that what is needed is “systems” from initial product and process design to metrics on

production performance and customer evaluations. Quality systems involve a closed loop process that shows data is evaluated and fed back into the system for the purposes of continuous improvement.

Risk Management

I am concerned that the guidance fails to adequately address the important subject of risk management. The guidance states “In a manufacturing quality systems environment, risk assessment is used as a tool in the development of product specifications and critical process parameters. Used in conjunction with process understanding, risk assessment helps manage and control change”. Establishing process control parameters based on risk and incorporating risk assessment in change control are indeed bona fide practices.

The guidance failed, however, to list other areas where risk assessments are needed. One area it is needed is in the evaluation of product and process non-conformities and in implementation of corrective and preventive actions (the CAPA program). Another risk assessment area not listed in the guidance is validation planning and execution (the Validation program). Product process parameters must be established utilizing risk management tools. This goes to both process development for clinical batches and more importantly in the area of design transfer of the product for commercial production. In real life the latter area is a major concern. If the rush to produce the three validation batches is done without consideration of the risks there are serious consequences later.

Management Controls

On a positive note I am pleased with the Guidance’s sections on Management. It is essential that senior management play a major role in assuring adequate and effective quality systems are in place. It may be worth stating in the Guidance that the Food, Drug and Cosmetic Act already places senior management in the role of assuring those quality systems are in place and are robust. The Park decision at the US Supreme Court reiterates the fact that executives are responsible for the company’s GMPs and quality system regardless of whether they had personal knowledge of the GMP deficiencies. These responsibilities are inherent – even without the Guidance.

Design Controls

One area that was not adequately addressed in the guidance is Design Control. While the guidance does mention design controls, it fails to mention the needed aspects of design control in product development. Design controls, such as those found in 21 CFR 820.30 (medical devices), are needed to ensure discipline is instilled in the development processes. There are specific steps and “gates” that the development process must pass through. These steps should be outlined by FDA and CDER in a formal document. The discipline that design controls provide will assure the public that the pharmaceuticals they consume were derived from adequately designed clinical batches. Design controls are especially needed when transferring drug products from research into production. Without design

controls there is a possibility that the drugs transferred from clinical batches to final production are not the same compound – due to inadequate controls in the earlier stages. Design controls should tighten the steps in drug development – with a result being consistency of the drug product and faster times to market.

I would suggest that the design control guidance delineate where FDA believes the regulated process begins. In other words, explain that the Research side of R & D is not FDA regulated, but the Development side is. Record keeping, production of clinical batches and associated quality system issues must be addressed by the guidance. If a state of GMP compliance is expected in the product development area, it should be clearly explained.

CAPA and Root Cause Analysis

Another area that the guidance failed to address is root cause analysis. During the handling of nonconformities and the evaluation activities it is essential that investigations be conducted to determine root causes. Corrective actions that follow should be based on the root causes. While it is not always possible to find root causes, every attempt should be made to determine root cause where appropriate. Language should be added to the non-conformity and corrective action sections to explain FDA's position. It is an expectation already that non-conformities (both product and process) be investigated to the root cause level and appropriate corrective actions be done. It is also becoming an expectation that some form of effectiveness verification be done on the corrective actions. FDA should step up to the plate and provide detailed guidance on the expected industry practice in this area.

Conclusion

I am grateful for having the opportunity to comment on this Guidance document. Hopefully FDA will review all the comments and make the necessary improvements in the Guideline – and go the next step of publishing a quality system oriented GMP for the pharmaceutical industry.

I can be contacted by email at TRW@QualityHub.com, by phone at 301-873-0950. I am willing to assist in development of the new Guidance and the GMP.

Sincerely,

Timothy Wells
Wells & Associates/QualityHub, Inc.
18400 Azalea Drive
Derwood, MD 20855
301-873-0950
Email: TRW@Qualityhub.com

CC: FDA Dockets - HFA-305 (Docket No. 2004D-0443)