

December 03, 2004



Division of Drug Information (HFD-240)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

RE: Docket No. 2004D-0443 – Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck & Co., Inc. has vast experience with drug and biological development and manufacturing partnered with the submission and approval of regulatory dossiers worldwide. As such, we welcome the opportunity to provide comment to this draft document intended to encourage the use of quality management system principles. We are encouraged by the FDA's approach of seeing current Good Manufacturing Practice Regulations (cGMP) as a part of a larger quality system. This along with the Agency's increased focus on using risk assessment in interpreting and applying cGMP during inspections is very consistent with modern quality systems.

We agree that it is helpful to the pharmaceutical industry to know the regulatory expectations of the quality system initiative. In addition to FDA, there are ICH documents including ICH Q8 (Pharmaceutical Development), ICH Q9 (Risk Management) and possibly ICH Q10 (Quality systems) that are in development. We are supportive of global harmonization of regulatory requirements and expectations and encourage the Agency to continue to foster harmonization.

In addition, we agree with the position of the Pharmaceutical Research and Manufacturers of America (PhRMA) in that the appropriate use of a robust quality system should qualify a manufacturer to make changes in the manufacturing process without seeking approval from the Agency. Therefore, it is of value for those robust quality system requirements to be clearly defined. In addition, we are supportive of the changes suggested by PhRMA and do not see a need to be redundant in addressing the same points. Therefore, our comments are intended to be in addition to those provided by PhRMA.

FDA has in the past used guidance documents, such as this one, to inform both the industry and their investigational staff of new interpretations of existing cGMP regulations. The use of mandatory language, such as “*must*,” was used when a particular statement was required by regulation and non-mandatory language, such as “*should*,” was used to show current Agency thinking while recognizing that other alternatives could also satisfy the intent of the regulation. This draft guidance is distinctly different in that it is intended to convey a number of expectations for a broader quality system than is required by cGMP regulations and changes the use of “*should*” to merely suggestions or recommendations if not followed by a regulatory citation (cite).

The draft document has a number of stated expectations that lack a specific regulatory cite, but are nonetheless requirements of cGMPs. In addition, some cGMP requirements are compounded in sentences with non-cGMP requirements. The following are specific examples but are not intended to be all inclusive:

1. Lines 518-521: “*The firm’s personnel should be adequately trained and monitored for performance according to their quality system, and the contract firm’s and contracting manufacturer’s quality standards should not conflict.*” (No regulatory citation.)

Comment: The statement that “*personnel should be adequately trained*” is clearly a regulatory requirement (21CFR211.25) while the following phrases are suggestions or recommendations.

2. Lines 674-683: “*Both the CGMP regulations (see § 211.110) and quality systems models call for the monitoring of critical process parameters during production.*”

- *Process steps should be verified using a validated computer system or a second person. Batch production records should be prepared contemporaneously with each phase of production. Although time limits can be established when they are important to the quality of the finished product (CGMP addresses this; see § 211.111), this does not preclude the ability to establish production controls based on in-process parameters that can be based on desired process endpoints measured using real time testing or monitoring apparatus (e.g., blend until mixed vs. blend for 10 minutes)*”.

Comment: Without regulatory cites for the first two sentences under the above bullet, these should be viewed as only suggestions or recommendations and not as cGMP requirements or expectations. Some process steps require second person verification or checks. We doubt that FDA investigators would see preparing batch records contemporaneously with each phase of production as being a mere suggestion.

3. Lines 543-547: “*In a modern quality systems manufacturing environment, the significant characteristics of the product being manufactured should be defined, from design to delivery, and control should be exercised over all changes. Quality and*

manufacturing processes and procedures — and changes to them — should be defined, approved, and controlled (CGMP also requires this; see § 211.100)."

Comment: It is not always clear as to whether a specific regulatory citation only applies to a specific sentence or whether it may apply to several sentences. This is particularly true when the latter may be viewed as a logical extension of the first. The phrase in the first sentence "*from design to delivery and control*" is very broad and when seen in conjunction with the second sentence raises questions as how broadly this cited regulation dealing with having written procedures will be interpreted by FDA investigators.

4. Lines 623-625: "*Procedures should also be established to encompass the acceptance, use, or the rejection and disposition of materials produced by the facility (e.g., purified water). Systems that produce these in-house materials should be designed, maintained, qualified, and validated where appropriate to ensure the materials meet their acceptance criteria.*"

Comment: Without regulatory cites for the above sentences, these statements would indicate that these are not cGMP requirements or expectations. However, cGMP regulations require procedures for these operations. When all cGMP requirements are not clearly identified, FDA investigators may not know which expectations are viewed as Agency expectations for cGMP regulations and which are not.

The draft document has a number of stated "*should*" expectations followed by specific regulatory cites indicating that they are cGMP requirements or expectations. The draft guidance states that it is not intended to create new expectations. However, many of the cited "*should*" statements create new expectations and may reasonably be seen by FDA investigators as providing the Agency's current thinking on cGMP regulations. The following are specific examples but are not intended to be all inclusive:

1. Lines 370-374: "*This approach is consistent with the CGMP regulations, which require manufacturers to develop and document controls for specifications, plans, and procedures that direct operational and quality system activities and to ensure that these directives are accurate, appropriately reviewed and approved, and available for use (see the CGMPs at §§ 211.22 (c) and (d)).*"

Comment: The inclusion of "*plans*" and "*procedures that direct operational and quality system activities*" are beyond wording in the cited regulation. Both phrases are vague and broad terms making it unclear as to how they might be interpreted by FDA investigators.

2. Lines 469-472: "*Personnel should also understand the impact of their activities on the product and the customer (this quality systems parameter is also found in the CGMP regulations, which identify specific qualifications (i.e., education, training, and experience or any combination thereof; see §§ 211.25(a) & (b)).*"

Comment: The inclusion of “*also understands the impact of their activities on the product and the customer*” is beyond the wording of the cited regulations. While the cited regulations require personnel to be qualified and familiar with the regulations, it is unclear as to how FDA investigators will interpret this guidance.

3. Lines 497-500: “*According to CGMP regulations, the QCU has the responsibility of reviewing and approving all initial design criteria and procedures pertaining to facilities and equipment and any subsequent changes (see § 211.22(c)).*”

Comment: The inclusion of “*all initial design criteria*” is beyond the wording of the cited regulation. It is unclear as to how FDA investigators will interpret this new expectation. We believe the wording in the regulation allows a company the flexibility as to when Quality’s input is most efficient and effective in the development process and that the Quality Unit approval is required for specifications and procedures impacting quality.

4. Lines 522-524: “*However, under the CGMP requirements, the QCU is responsible for approving or rejecting products or services provided under contract (see § 211.22(a)).*”

Comment: The exclusion of the word “drug” before “*products*” and inclusion of “*services*” expands the scope of the regulation. It is unclear as to whether FDA investigators will include non-drug products or which contracted services will be seen as requiring the Quality control unit approval.

5. Lines 604-608: “*The CGMP regulations require either testing or use of a certificate of analysis (COA) plus an identity analysis (see §§ 211.22 and 211.84). In the preamble to the CGMP regulations (see comment 239 in the preamble), these requirements were explicitly interpreted. The preamble states that reliability can be validated by conducting tests or examinations and comparing the results to the supplier’s COA.*”

Comment: The cGMP regulations were paraphrased in a manner that along with discussion could result in FDA investigators interpreting the cGMP as always requiring testing or a COA on acceptance of supplier material when in fact 21CFR211.84(a) states “tested or examined, as appropriate” which provides an alternative to testing when appropriate.

6. Lines 770-771: “*Customer complaints should be handled as discrepancies and be investigated (CGMP addresses this; see § 211.198).*”

Lines 1025-1026: Lines 1025-1026: *“Discrepancy - Datum or result outside of the expected range, an unfulfilled requirement; may be called non-conformity, defect, deviation, out-of-specification, out-of-limit, out-of-trend, etc.”*

Comment: The CFR (21CFR211.198(a)) states “Written procedures . . . shall include provisions for review . . . of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation . . .” Not all customer complaints are “discrepancies” as defined in the draft guidance and while all complaints must be reviewed or evaluated, not all complaints require investigations.

7. Lines 818-819: *“(FDA’s policy is to not routinely review or copy reports and records that result from internal audits per Compliance Policy Guide 130.300)”*

Comment: The draft guidance paraphrases the Compliance Policy Guide (CPG) in a manner that may result in FDA investigators believing the Agency policy is to review internal audits as long as such are not routinely done. Actually, the CPG states that such inspections of internal audits will not be done during routine inspections and cites only specific instances when such may be done and in practice, a rare occurrence.

8. Lines 794-795: *“Although the annual review required in the cGMP regulations (§ 211.180(e)) call for review of representative batches on an annual basis; quality systems calls for trending on a regular basis.”*

Comment: The cited requirement is for a representative number of batches rather than representative batches. As written, the implication is also that under a broader quality system such trending should be on a “regular basis” rather than annually but offers no indication as whether it should be more or less frequent.

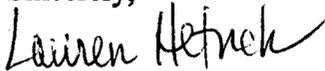
Merck & Co., Inc. is supportive of FDA’s efforts to develop a quality system model for the pharmaceutical industry. However, we have concerns about how this guidance document will be seen by FDA investigators conducting inspections. If FDA moves forward with this document, we suggest that all references to cGMP regulations be deleted and the guidance clearly state that it is intended only to be a model quality system. Further, that while encompassing some of the requirements of the cGMP regulations, the guidance contains many suggestions and recommendations that go beyond the cGMP regulations and therefore should not be used during inspections. The pharmaceutical industry will recognize those aspects of the quality system model that are covered by cGMP regulations and those that are recommended that go beyond cGMP regulations.

Docket No. 2004D-0443

Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations-page 6

We appreciate the opportunity to share our comments with respect to FDA's Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. Please do not hesitate to contact me at (484) 344-4812, should you have any questions.

Sincerely,



for

Taryn Rogalski-Salter, PhD

Director, Regulatory Policy

Worldwide Regulatory Affairs, Vaccines and Biologics