

Alice E. Till, Ph.D.
VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS



December 3, 2004

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

Re: Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations [Docket No. 2004D-0443, 69 *Federal Register*, 59256 (October 4, 2004)]

Dear Madam/Sir:

The following comments on the subject draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than \$32 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA is very supportive of the Agency's desire to define quality systems approaches for the pharmaceutical industry through the new DRAFT guidance, *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulation*. In general, we see this as a positive approach to modernizing quality systems throughout the industry and to creating approaches that encourage manufacturers to implement improvements to their products, processes and systems. The intention of the document is well defined; it is put forth as recommendations, not regulation, and still provides industry with direction on the Agency's current thinking on this topic.

The document brings in many of the concepts already defined in the Quality Systems Regulations and does not take a totally different direction. It is obvious that much effort has been invested in ensuring the document links to the drug regulations, 21 CFR Parts 210 and 211. This effort is especially welcomed since the inspection program will be geared to these regulations.

PhRMA supports the need to harmonize CGMPs globally, wherever possible, and will continue to work with the Agency, other regulators and industry groups to achieve this. In addition, the recognition that regulatory submissions may not be needed when a manufacturer with a robust quality system has the appropriate process knowledge to

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implement a change is a major step forward. This has the potential to remove many of the barriers that make change so difficult in today's environment.

General Concerns/Recommendations

PhRMA agrees with the desire to harmonize CGMPs globally wherever possible. With the ongoing work to develop ICH Q8 Pharmaceutical Development, ICH Q9 Risk Management and possibly ICH Q10 on quality systems, it is critically important that the direction defined in these documents be consistent, and not conflict with this guidance. Since the ICH documents are not finalized at this point, we request that the Agency be flexible with this guidance document to ensure it stays consistent with the ICH documents as they are developed. PhRMA will continue to support, as it has in the past, the ongoing efforts to bring the ICH documents to completion.

The potential that changes could be made to a manufacturer's facility, equipment or process based on the manufacturer's knowledge of the process and the robustness of its quality systems is an approach that PhRMA strongly supports. However, to prevent potential problems and misinterpretations, we believe that the process for achieving this should be further defined. This would provide industry with the necessary direction and would eliminate potential compliance issues in the future.

We agree with the Agency's statement that "This document is not intended to create new expectations for pharmaceutical manufacturing that go beyond the requirements laid out in the current regulations nor is the guidance intended to be a guide for the conduct of FDA inspections". Because some of the specific concepts discussed in the guidance document may be new to some companies, the document may cause some companies to institute changes consistent with the guidance. PhRMA believes it is critically important that the Agency's position be thoroughly communicated to investigators so the document does not become an inspection tool. Additionally, we recommend that the specific, but only partial, inclusion of sections from 21CFR 210/211 may mislead readers into believing that the content of this guideline reflects the Agency's current interpretation of the GMP regulations. We suggest removing these partial quotations from the document and instead providing citations to the regulations.

Since the document is intended as guidance only, the use of the word "should" is appropriately used in the document. There are, however, numerous parts of the document where the word "expected" is used outside of the 21CFR 210/211 requirements. PhRMA recommends that the document be modified to ensure the word "should" is used where there is no direct relationship to the regulations.

The concept of risk management/risk assessment is key to the Agency's approach and to a robust quality system. The document, however, is very brief on details and direction for risk management. PhRMA believes that the risk management section of the document should be expanded to further describe this key activity and how it could be used in a robust quality system.

Specific Comments by Section and Line Reference

I. Introduction

No comments.

II. Background and Purpose

Line 72: Delete the phrase “that are fully compliant with CGMP regulations” Since it implies that if this document is followed, manufacturers can be fully compliant. There are numerous other documents, requirements, and regulations that manufacturers must follow to be fully compliant.

Lines 98-103: PhRMA agrees with this section, however, the requirements for how this would take place will need to be defined.

Line 116: Add “(API’s)” after the word “components”. This further clarifies the scope for the reader.

III. CGMPs and the Concepts of Modern Quality Systems

Line 167: Delete “and Risk Assessment”. Since risk assessment is a part of risk management, only Risk Management would need to be referenced. This also maintains consistency with ICH Q9.

Lines 169-173: More information and direction on the use of risk management would be helpful here.

Line 196: The statement “This means a manufacturer is empowered to make changes...” needs more definition. As mentioned above, this possibly would require a guidance document to provide direction and prevent compliance issues.

Line 210: Delete the word “all”. As written, it suggests that every document is reviewed and approved by QA, which may not always be the case.

Line 211: Change “...performing trend analyses” to “... evaluating trend analyses.” Since QA may not actually perform all of the analyses, evaluation better describes the function.

Line 232: Change “... records and investigating any unexplained discrepancies” to “... records, reviewing and approving investigations for any unexplained discrepancies, and authorizing product release.” Since Quality may not perform all of the investigations, this better describes the function. Authorizing product release is a key responsibility of the Quality department and should be mentioned.

Line 233: Add a new line (fifth dot point) “Ensuring a quality review process is in place.”

Line 235-238: Delete the section “In very small operations...standards have been met.” Replace with “The number of individuals assigned to the quality unit should be sufficient to meet the requirements of 21CFR §211.22 and other applicable regulations, although the number may be reflective of the size of the operation. The quality unit is accountable for implementing all the controls and reviewing results of manufacture to ensure that product quality standards have been met.” Referring to quality units that consist of a single person may cause confusion among manufacturers.

Lines 234-238: Move this section to precede line 222. This paragraph fits better with the paragraph ending on line 220 and this change improves the flow of the document.

IV. The Quality System Model

Lines 286-291: Delete the section beginning with “As already explained...specific GMP regulations. . .” this is redundant with what was included earlier in the document.

Line 319: Delete “Senior”. Since managers at all levels of an organization set priorities and develop action plans, this should not only be limited to senior managers.

Line 356: Change to “...the Agency recommends that senior managers ensure that the quality system *that is designed and implemented* provides...” Since the senior managers may not design and implement themselves, this provides a better description.

Line 363: Change “policies” to “requirements”. This more accurately reflects the point that requirements may be much broader than policies.

Line 368: Delete “record”. This is redundant with the word record that appears later in the sentence.

Line 370: Change “activities” to “requirements”. The word "activities" is not definitive enough and is too open to interpretation.

Line 407: Change to “Under a quality system, the review should consider the following examples. . .” Manufacturers should have flexibility with what is included in the management review. As previously stated, it can be interpreted that everything listed must be included.

Line 418-419: Change to “...reviews should take place *at a frequency appropriate for the system being reviewed.*” As previously worded, it suggested mature systems would need to be reviewed less frequently but that may not always be the case.

Line 422: Change “typically” to “may”. Not all review outcomes will result in the examples shown.

Line 462: Change “cross-cutting” to “cross-functional”. This term better describes the intent of the effort.

Line 482: Change to "...training programs that *may* include the..." All of the items listed may not always be necessary.

Line 489: Delete "supervisory". The term "managers", by itself better describes the need, and the term "supervisory managers" is not included in the Glossary.

Line 497: Delete "all". This better defines the need since not all design criteria may be approved by the QCU.

Line 503: Change to "...maintained *and operated in a state of control.*" Provides a more complete description of needs beyond only contamination and mix-ups.

Line 505-507: Delete the sentence "The CGMP regulations...focus only on testing equipment." The sentence implies that quality systems are not focused on process equipment when in fact, they are.

Line 521: Change "officers" to "management". This keeps terms consistent with the rest of the document.

Line 523: Change to "...the QCU is responsible (*as defined in the contract or quality agreement*) for approving..." This clarifies that the contract manufacturer or the original firm may have responsibility, which is dependent on the quality agreement in place.

Line 549: Change to "This documentation *may include.* . ." Since not all of the items listed will apply in all cases, this better describes the need.

Lines 569-573: Delete the sentences "Packaging and labeling controls...FDA recommends that,". Begin the first sentence with "As part of the design process..." Since packaging and labeling controls are a significant part of industry's quality systems, this eliminates any confusion that they are not.

Lines 581-589: Move this paragraph to line 541 under I. *Design and Development Product and Processes*. This paragraph fits better in this section rather than packaging and labeling.

Line 629: Delete "certain". Since changes should be reviewed by quality, this clarifies the need and eliminates potential confusion.

Lines 651-652: Change to "...a manufacturer should be able to *ensure the process is in control through continuous verification or process validation.*". With the concepts of continuous verification, process validation may not be necessary.

Line 659-660: Delete the sentence "Thus, in accordance...that continues." This sentence is redundant with earlier sections and adds confusion as to when continuous verification is used in place of process validation.

Line 674: Change to "...critical process parameters during production. *For example. . .*"
To clarify that these are only a few examples of monitoring requirements.

Line 677: Change to "*Critical* process steps..." This will clarify that not all process steps may need to be verified.

Line 690: Change to "...meet their *critical process* parameters." This will clarify that not all parameters need to be measured or monitored.

Line 702: Change to "Are *data* collection methods documented?" This will clarify the intent of the sentence.

Line 719: Change to "...should be based on *its significance and on* monitoring and evaluating..." This will clarify that not all changes carry the same level of significance or risk.

Line 730-731: Change to "...should be *based on sound and justified reasons.*" This eliminates potential confusion with using statistics to invalidate results.

Lines 733-735: Move this paragraph to line 566 under *Design and Develop Product and Processes*. Shipping requirements and handling should be considered much earlier in the lifecycle.

Line 750: Change to "...important to measure *critical process* parameters and the *critical* product attributes..." This clarifies that not all parameters or attributes are critical.

Lines 760-761: Change to "...consequences to process *control*, product quality, safety, *efficacy*, and *product* availability..." This clarifies the intent of the sentence.

Line 808: Delete "at least annually." This allows flexibility in the design of a firm's audit program.

Line 821: Per earlier comments, the section on Risk Management should be further defined to provide direction and examples. Risk management should also be included in other applicable sections with examples of how it could be used.

Line 832: Change "reiterative" to "iterative".

V. Conclusion

Lines 892-903: It is not clear where each of the examples is "discussed in detail" in the document. References by each dot point would aid the reader since it is not clear where each point is discussed.

Glossary

Line 1027: Add a definition for “management (managers)” which is a term that is used throughout the document.

We appreciate the opportunity to comment on this draft guidance and thank you in advance for your consideration of these comments as you finalize the guidance. Please contact me if you have any questions.

Sincerely,



Alice E. Till, Ph.D.

CC M. Caphart (CDER)
R. Sausville (CBER)
J. Liang (CVM)
P. Maroney-Benassi (ORA)