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US Food and Drug Administration  
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5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**REF: Draft Guidance for Industry: Quality Systems Approach to  
Pharmaceutical Current Good Manufacturing Practice Regulations,  
September 2004, submitted to Docket # 2004D-0043 CDER 2004 115**

Dear Sir or Madam:

PDA is pleased to provide comments on the FDA Draft Guidance for Industry "Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations," issued in September 2004. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality. PDA wishes to thank the Agency for the opportunity to provide comments on this document.

We believe this guidance provides industry a significant impetus to change their manufacturing philosophy from a reactive post-manufacturing quality testing regimen into one directed toward a manufacturing operation based on science and technology, with quality designed into the process and product. It is important for both industry and the Agency to have flexibility when applying this guidance irrespective of the size of the firm. As PDA is a member-based organization, this is an important consideration, since its members can be employed at large, medium and small manufacturing firms.

Please find detailed comments in the attached spreadsheet (Appendix A) and suggested revisions to Section III F (Appendix B). In addition, PDA would like to offer the following general comments:

**Point #1: Globalization (reference lines 94 to 97)**

PDA applauds FDA in its support of efforts to harmonize quality systems approaches to drug manufacture across the globe. PDA looks forward to participating in the effort through the pre-established mechanisms for global harmonization.

**Point #2: Regulatory Flexibility (reference lines 98 to 103)**

The Guidance is clear as to the benefits realized by a firm which develops and implements quality systems consistent with the principles stated in this guidance. However, it is not clear the mechanisms by which a firm can implement changes without the need for regulatory submissions. PDA welcomes the process of less strict regulatory submissions and offers to participate in development of such initiatives.

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**Point #3: Clarification of Scope (reference line 113 to 116)**

The draft states “this guidance applies to manufacturers of drug products (finished pharmaceuticals)”; it makes no mention of Active Pharmaceutical Ingredients (APIs) or bulk biologicals. As the spirit of quality systems should be applicable to all stages of manufacture and recognizing there are no conflicts between this document and Q7A (Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients), PDA recommends that API and bulk biologic manufacturing be considered for inclusion in the list of the types of manufacturers affected by this guidance. Because many sites house both API/bulk and drug product manufacturing, it is imperative to have a clear message from FDA that common quality systems should be supported to assure effectiveness and efficiency. With regard to biological products, PDA recommends that FDA also provide guidance regarding the applicability of the Quality System approach to manufacturers engaged in “Shared” or “Divided” manufacturing arrangements.

The draft guidance also states that it “may also be useful to manufacturers of components used in the manufacture of these products.” This implies suppliers are included in the scope. Since not all suppliers are FDA approved or subject to 21CFR Parts 210 and 211, PDA recommends that this sentence is removed from the guidance.

**Point #4: Change Control to Change Management (reference line 185)**

PDA recommends replacing Change Control with Change Management. The term change management contains the concept of inter-relatedness of process, specification, and software changes in a multi-disciplinary approach. PDA recognizes the term "change management" encompasses more than does "change control" and feels the term is consistent with the concepts discussed within this document, specifically moving beyond quality control to a quality system approach.

**Point #5: Inspectional Authority (reference line 290 and 304)**

FDA is clearly articulating expectations for management, including senior management of a firm. Enlightened senior management will see quality systems and risk management can help the firm achieve the goals of quality, cost and service. We acknowledge a greater responsibility is being placed on industry. However, along with these new expectations is a concern there will be difficulty limiting inspections to only specific CGMP regulations. FDA will have to provide training to their pharmaceutical inspectorate as to how to conduct a review of the application of risk management approaches which are outside of current regulatory requirements. An absence of these systems should not be an inspectional observation provided there is compliance with 21CFR Part 211.

**Point #6 : Implementation (reference 808, multiples points)**

On line 808 there is a requirement to audit the entire system at least annually. This requirement is difficult and onerous if not impossible to do well. It also seems grounded in the traditional “checklist” approach to quality. PDA does not see this as a necessary or value-added requirement. Two of the cornerstones of a contemporary quality system are: i) management is responsible to build in ongoing, real time (or nearly real time) monitoring of the critical controls of the process and product; and, ii) management is responsible for using process/product monitoring data and the operations knowledge base to effect continuous and timely improvements. Routine monitoring of key metrics coupled with the evaluation of the quality system by internal audits provides continuous assurance the quality systems are working.

**Point #7: GMP references**

PDA notes there is an inconsistent level of detail when referencing specific GMP requirements. PDA recommends that the examples of specific GMP requirements and recommendations for maintaining quality be limited and only in support of a particular point with regard to the implementation of a quality system approach.

The concepts discussed in this guidance are far-reaching and of great importance for reaching the goals set forth by FDA in the "GMP's for the 21<sup>st</sup> Century" initiative. All parties will benefit from continued dialogue around clarification, interpretation, and implementation of these concepts. PDA looks forward to continuing to contribute to this discussion. PDA also offers to work with FDA to support forums for such dialogue.

Yours sincerely,

A handwritten signature in cursive script that reads "Victoria Ann Dedrick". The signature is written in black ink and is positioned above the typed name and title.

Victoria Ann Dedrick  
Vice President, Quality and Regulatory Affairs  
PDA

**Appendix A: PDA Comments on the Draft Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**

Section	Guidance Line	Comment	Rationale
	39	Many pharmaceutical manufacturers are implementing quality systems and risk management approaches that are not specifically addressed in existing regulations. A Quality System Guidance Development working group (QS working group) was formed to compare the current CGMP regulations, which call for specific quality management elements, to other existing quality management systems. The QS working group mapped the relationship between CGMP regulations (parts 210 and 211 and the 1978 Preamble to the CGMP regulations[2]) and various quality system models, other quality publications, and experience from regulatory cases. The QS working group determined that, although the regulations do provide great flexibility, the CGMP regulations do not consider all of the elements that today constitute most quality management systems. The CGMP regulations and other systems differ somewhat in organization and in certain constituent elements; however, they are very similar and share underlying principles. For example, the CGMP regulations stress quality control. More recently developed quality systems stress quality management, quality	While the historical background information regarding the Pharmaceutical CGMPs for the 21st Century Initiative is interesting, once the guidance is finalized, it will rapidly become obsolete. It is suggested that much of the first paragraph be removed/deleted from the body of the text. A preamble, if one is created, could be a better place for this useful historical information.
	44	Replace manufacturing technologies with the phrase in italics: There have been many advances in "manufacturing technology and science" and in our understanding of quality.	This statement would then be consistent with language from PQRI.
IIB:	98	Please clarify how a firm can handle may handle different types of changes without the need for regulatory submission.	Please refer to our cover letter Point # 2.
II C	113	The document states this guidance "applies to manufacturers of drug products (finished pharmaceuticals) including products regulated". It is highly desirable to include Active Pharmaceutical Ingredients in the scope.	Please refer to our cover letter Point #4.
	148	The QS should apply throughout the entire life cycle of the product or service. Fundamental to the QS is an organization that ensures and integrated approach to satisfy the particular safety and performance needs of the specific manufacturer, product and user-market. In the CGMP regulatory context, the quality system affirms the interrelatedness of the five other major systems detailed in the Drug Manufacturing Inspection Compliance Program and establishes the infrastructure to support their effective functioning and continuous improvement.	In place of the adjectives (robust, modern, etc) describing the quality system, a philosophical discussion of the quality system is warranted.
IIIA	154	The definition of quality is inconsistent with the definition provided in the Glossary. "Achieving Quality" is much more than merely meeting product specifications. A better definition is required.	If "achieving quality" is defined as it is within this document, it would not be as advantageous for a firm to expand resources beyond those required to meet product specifications for identity, strength and purity and is counter-intuitive with many of the concepts defined by this guidance. "Achieving Quality" in context with "Quality by Design" goes well beyond the definition in this document.

**Appendix A: PDA Comments on the Draft Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**

Section	Guidance Line	Comment	Rationale
	171	Add phrase in italics: Risk assessment is also used in determining the need for discrepancy investigations and corrective action "and for changes to existing processes".	As written, risk management is part of setting specifications and process parameters as well as determining the need for a discrepancy investigation and corrective action. Risk Management, in a life cycle approach can assess and mitigate the risk of a change to a process or specification. Risk mitigation methods are based on process/product knowledge as well as priority.
III E	185	Change "Change Control" to "Change Management".	Please refer to our cover letter Point #5.
	195	change "towards continuous improvement" to "towards innovation and improvement".	One of the basics tenets of the FDA's initiative is to enable innovation in the manufacturing science of pharmaceuticals.
	204	Replace Section F "The Quality Unit" as written with the recommended section located in Appendix "B".	PDA believes the language in the supplied rewritten section is clearer and consistent with current expectations and practices.
	241	There should be a comparison of the relationship between the systems in the Systems Based Inspection Model (CPGM 7356) and the Quality Systems Model discussed in this document.	This will assure there is no conflict between the two documents and/or the two approaches.
IV	290	If FDA regulatory and routine GMP inspection coverage will remain focused on the specific CGMP regulations, how will inspections incorporate the application of risk management which may be outside of regulatory requirements?	Please refer to our cover letter Point #6.
IV A	304	There is a concept underlying in this section of senior management responsibility and corporate knowledge and initiatives to address compliance issues. As part of inspections, FDA can use this concept to evaluate a non-compliant situation in concert with risk management (risk mitigation) tools.	Please refer to our cover letter Point # 5.
	306	Please define Management and Senior Management.	CFR 820 uses a different term "Management with Executive Responsibility". Defining the terms would provide greater clarity for all persons trying to interpret the guidance.
	367	"It is recommended under a modern quality systems approach that a formal process be established to submit change requests to directives".	PDA is unclear as to which directives FDA is referring to. Please clarify.
	395	change "identify resources" to "allocate resources".	In order to have an effective quality system, resources must be allocated not just identified.
	405	add process to "an assessment of the product and process".	This acknowledges that quality systems should address the process not just the product meeting specifications.
IVA5	428	A reference to FDA's policy of not reviewing internal audit results and supplier audits during inspections should be broadened to include for management reviews as well.	Routinely making these types of internal records available to FDA investigators during inspections will compromise their value to the firm.

**Appendix A: PDA Comments on the Draft Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**

Section	Guidance Line	Comment	Rationale
IVC3	613	Please include phrase in italics: The quality systems approach also calls for the auditing of suppliers on a periodic basis "using a risk based approach for the scheduling and necessity of the audits".	The Guidance should recognize that it is neither necessary nor practical for firms to routinely include all suppliers in an audit program. Using a risk-based approach, manufacturers should and do determine which of their suppliers require audits and how frequent these audits should be.
	622	If quality systems approach is also meant to be built into the culture and operational approach even in development (especially late stage) - the use of "approved" sources may be confusing - as they may not be included in a market application at the time a firm is implementing the quality system. Perhaps the document needs to refer to "acceptable or appropriately audited/monitored vendors - and/or those listed in approved market applications".	If the document is meant to be applicable to development activities as well, this will allow for flexibility for implementing QS during development.
	630	Change "quality control unit" to quality unit.	This becomes consistent with the distinction between Quality Unit, QC and QA described in Section III F.
	646	Change from "process weakness" to areas of "higher risk".	The concept of higher risk is consistent with this document.
	730	Delete word "statistically" from "invalidation of test results should be scientifically and statistically sound and justified.	This is the first time FDA has required that statistics be used to justify invalidation of a test result. This additional requirement is not consistent with other draft guidances and does not belong in this document.
IVC5	770	Delete the phrase "be handled as discrepancies and".	Customer complaints should not automatically be considered discrepancies.
	808	Delete the requirement the "need to audit the entire system at least annually".	Please refer to our cover letter Point 6.
IV D	823	Add phrase in italics: Effective decision making in a quality systems environment is based on an informed understanding of quality issues and "their risk to patients."	Addition of risk to patients is consistent with the concepts in the FDA GMPs for the 21st Century initiative.
V	889	Change "quality professionals" to "pharmaceutical manufacturers".	All pharmaceutical operations personnel must be responsible for the quality of the products and processes.
Glossary	1022	Recommend changing the definition to "a person or organization (internal or external) that receives the output of a process anywhere along a product's life cycle."	Clarification; recognizes that all processes have inputs and outputs.
Glossary	1029	Delete the second sentence.	It is not clear that metrics can be qualitative.
Glossary	1047	As previously mentioned this definition is inconsistent with the one provided in the body of the Guidance at Lines 154 – 157.	This seems a better definition than "meeting specifications".
Glossary	1053	Provide a better definition of "Quality Control". One possibility might be "those activities undertaken to measure or test the attributes of a product or service".	Quality Control is generally regarded as the testing activities undertaken. Other measures taken to ensure reproducibility and meeting requirements are more generally viewed as Quality Assurance.

**Appendix A: PDA Comments on the Draft Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**

Section	Guidance Line	Comment	Rationale
Glossary	1071	Change definition of Quality System to as follows: integrated processes for directing, monitoring, investigating and improving operations within a firm. The Quality System (QS) should assure that processes are oriented toward customer satisfaction, are conducted methodically, and emphasize decision-making based on factual information. These formalized business practices characterize the firm's commitment and culture regarding quality, and define the necessary resources and practices for achieving quality in its goods and services.	To provide the reader with an understanding of the broad scope and philosophy of the quality system.

## Appendix B

### F. The Quality Unit

Many of the quality systems ideas described in this section correlate very closely with the CGMP regulations (refer to the charts later in the document). Current industry practice generally divides the responsibilities of the Quality Control Unit (QCU), as defined in the CGMP regulations, between quality control (QC) and quality assurance (QA) functions.

- QC usually consists of component, in-process and finished product testing to evaluate the performance of the manufacturing process, and to ensure adherence to proper specifications and limits.
- QA primarily includes the review and approval of all procedures related to production, maintenance and control laboratories, and review of associated records, and approving or rejecting components, in-process materials and drug products.

This guidance uses the term *quality unit*<sup>1</sup> (QU) to reflect modern practice while remaining consistent with the CGMP definition in 21 CFR 210.3(b)(15) and its role as defined in 21 CFR 211.22. The concept *quality unit* is also consistent with a quality systems approach in assuring that the various operations associated with all systems are appropriately conducted, approved, and monitored. However, the quality unit is not meant to take on the responsibilities of other units of a manufacturer's organization, such as the responsibilities handled by manufacturing personnel, engineers, and development scientists.<sup>2</sup> The quality unit's activities do not substitute for, or preclude, the daily responsibility of manufacturing personnel to build quality into the product

Other responsibilities of the quality unit are consistent with a quality system approach and include, but are not limited to:

- Ensuring that controls are implemented and completed satisfactorily during manufacturing operations
- Ensuring that developed procedures and specifications are appropriate and followed, including those used by a firm under contract to the manufacturer
- Performing audits and trend analyses.
- Ensuring that any unexplained discrepancies are properly investigated

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<sup>1</sup> Generally, the term *quality unit* is used in this guidance. However, *quality control unit* is used when directly quoting parts 210 and 211.

<sup>2</sup> See Reference #1, comment 91.