



## Pfizer Global Manufacturing

**Monday, November 22, 2004**

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fisher Lane, Room 1061  
Rockville, MD 20752

**Re: Draft Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, September 2004, submitted to Docket #2004-22206**

Pfizer recognizes the great effort and forethought the FDA has put forth in the publication of the draft guidance and appreciates the opportunity to provide comments to further clarify and strengthen the proposed guideline.

Please find our specific comments in the attached Spreadsheet (Attachment 1) and the following general comments:

**Item A: Transitioning from Compliance Systems to Quality Systems**

Achieving quality is defined in this document as "achieving identity, strength, purity, and other quality characteristics designed to assure the required levels of safety and effectiveness". Where robust quality systems are in place, the dependence on end product testing becomes diminished. The definition of quality and achieving quality should be based instead on the quality systems and process knowledge that predict the above mentioned characteristics as well as availability and patients requirements. Quality then progresses into a more probabilistic definition. This will necessitate transitioning from compliance systems to quality systems. For example, trending of data is identified as an important element of a good quality system. However, much of the data collected is for compliance systems and can not be meaningfully trended.

**Item B: Change Management as opposed to Change Control (line 708)**

In an environment supportive of a quality systems approach rather than a quality control approach, it is necessary to describe change management in lieu of change control. Change in the current pharmaceutical environment can no longer be considered in isolation as a single event. Rather, the result of change has many different impacts such as training, validation, stability, and regulatory compliance. Prior to implementing, and as part of assessing a change, a site must understand all these aspects and their interactions and consequences. This understanding occurs as a site increases its process knowledge. A site can not review a specific change without evaluating all the impacted and interacting systems.

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**Item C: Implementation of Regulatory Flexibility (reference Line 98)**

The guidance discusses and offers the concept of regulatory flexibility with respect to implementing changes. There is no discussion as to how these changes will be implemented. Implementation can occur through several means such as a supplement, a comparability protocol, or implementation through the firm's own quality system. Firms committed to investing the time and resources to implement a quality systems approach should be able to realize the benefits of regulatory flexibility. This guidance is not the place for this amount of detail, however, the Agency should prioritize the development of further guidance on this critical topic.

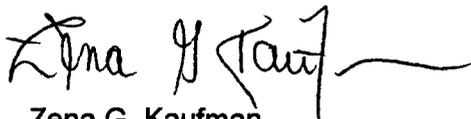
**Item D: Active Pharmaceutical Ingredients (line 116)**

Components (§ 210.3) are defined as any ingredient intended for use in the manufacture of a drug product. This guidance states the application of this guidance may be useful to manufacturers of components. Specific to the manufacture of Active Pharmaceutical Ingredients, there should be acknowledgement that by implementing a quality systems approach, API manufacturers can also take advantage of the regulatory flexibility discussed in lines 98 through 103. For manufacturers of components, other than Active Pharmaceutical Ingredients, implementation of this guidance should be optional and risk based.

**Item E: Linkage to the Pharmaceutical Inspectorate (reference line 290)**

Two of the key achievements of the FDA GMP Initiative are the development of the Pharmaceutical Inspectorate and the PATRIOT team. The PATRIOT team has provided cross functional training for defined inspectors who will be using the guidance during inspections. In an analogous manner, inspectors will need to be able to assess the application of principles within this guidance falling outside of regulatory requirements. These inspectors will need to be able to evaluate application of risk management processes transferring between what is required within the regulations and what is interpreted as current GMPs. Inspections must still be grounded in the actual regulations. The agency should give careful consideration to how to incorporate risk management and other optional practices into the pharmaceutical inspectorate curriculum.

Sincerely,



Zena G. Kaufman,  
Sr. Director Regulatory Compliance Initiatives, Pfizer Global Manufacturing  
Pfizer Inc.

Section	Guidance Line	Comment	Rationale
I	24	Suggest adding to the phrase to the sentence ending with parts 210 and 211 "and to continuously improve the quality and compliance of the product in a methodical manner".	Implementation of quality systems goes beyond fulfilling GMP requirements.
II.A.	47	The agency states that it saw a need to address the harmonization across other regulatory systems (both within and external to the CDER). Pfizer agrees this is a valuable goal and supports an initiative to harmonize across other regulatory systems within FDA and across other agencies.	
II.B.	71	From the guidance: "This guidance describes a comprehensive quality systems model, which, if implemented, will allow manufactures to operate robust, modern quality systems that are fully compliant with cGMP regulations". In order to achieve this there needs to be more focus, if not the main focus on how to design, implement, operate, or improve systems. This needs to be discussed in a future guidance.	FDA is defining what quality systems are needed but not what good quality systems are and how to implement quality systems.
II.B	92	There should be further harmonization across the QSR (CFR 820) and other non-US requirements in the form of guidances. The ICH process provides an excellent vehicle for harmonization.	Harmonization of GMPs, ISO9000, non-US Pharma requirements, and medical devices are admirable goals. While this guideline is an admirable step forward in the goal of harmonization, it is only a beginning not an endpoint
	103	Please add in the phrase in italics: In addition, an effective quality system, by lowering the risk of manufacturing problems, may result in shorter and fewer FDA inspections "and the ability to enact changes with greater regulatory flexibility"	Please refer to Item C in the cover letter
II C	113	"...applies to manufacturers of drug products (finished pharmaceuticals) including products regulated...." Please revise to allow the application to Active Pharmaceutical Ingredients	Please refer to Item D in the cover letter
II	118	There will need to be significant training of inspectors who will be able to correctly assess quality systems and to separate comments on quality systems from observations related to GMP deficiencies.	Please refer to Item E in the cover letter
III	146	There is no definition as to what constitutes a system. For example a system has system design, quality planning, inputs, outputs and a system owner.	In order to fully understand how to develop and implement quality systems, there need to be a basic understanding of a system
III A	156	Please broaden definition of achieving quality to include concepts discussed in this document such as risk management.	Please refer to Item A in the cover letter

III. B	161	Quality by design definition should include formulation as well as process design	
	171	Please include the concept of risk assessment for changes to existing processes	As written risk management is part of setting specification and process parameters as well as determining the need for 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.
III D	175	CAPA needs to be presented in a clearer manner. Corrective actions are those applied to the current discrepancy (such as repacking, rework, etc.). Preventive actions are those designed to prevent recurrence.	FDA lists root cause analysis with corrective actions to prevent recurrence. Preventing recurrence is Preventive action not corrective action. Furthermore, preventive action is listed as action to prevent initial recurrence. This can be more correctly listed as root cause analysis to prevent recurrence.
III D	181	Please add the phrase in italics: Remedial corrections "to determine actions necessary for impact to all potential implicated batches".	The other two bullet points clearly describe how the CAPA is used in operations
III E	185	The example of material variability is not presented as an example, but should be. In the text later in the document it would be advisable to have more guidance on what kind of changes a manufacturer is empowered to make.	Pfizer is pleased to see FDA understands a change management system not only as a requirement to prevent unintended consequences as stated. The main purpose of change management is to allow for implementation of changes to facilitate continuous improvement.
	185	This section should be clarified to state that in modern quality systems these are the roles for management. Please add being part of the management team fulfills the role the quality unit can have to assure systems put in place meet the CGMP requirements.	
III E	185	Please change the term "Change Control" to "Change Management"	Please refer to Item B in our cover letter.
	196	Please add "ability to measure the effect of a change" to the basis by which a manufacturer is empowered to make changes	An important aspect of change management is the ability to assure the change is not detrimental to the overall quality. Without the ability to measure the effect of a change, a manufacturer can not determine the impact.
III F	207	Please add in the phrase in italics: QC usually consists of testing of selected in-process materials, "raw materials" or "components" and finished products...	Testing of raw materials and components is an important aspect of the QC function. Variability in raw materials and components can affect the product and process. The addition of these items completes the listing of items tested throughout the process.
III F	217	"The cGMP regulations specifically assign the quality unit the authority to create, monitor, and implement quality systems." Please expand to include cross functional teams instead of just the quality unit.	Quality systems are for the most part cross functional systems. Therefore cross functional teams are required to create, monitor, and implement them. Also since senior management is ultimately responsible for the quality system, they should monitor them.

IIIF	222	Validation and Quality Planning should be added to this statement.	These are important aspects of a quality system.
	229	Add "raw material" or "component's following the word "rejecting"	Release of raw materials and components is an important aspect of the QC function. Addition of these items completes the listing of items tested throughout the process
III F	230	Add the word "other" prior to the word "manufacturing"	To clarify that the quality unit although separate is part of the overall manufacturing operation
	232	Change "reviewing production records and investigating any unexplained discrepancies" to "actively participating in the investigation of an unexplained discrepancy"	The primary responsibility for investigating unexplained discrepancies should be in the area where the discrepancy occurred. QA should participate and facilitate the investigation but not be solely responsible for the investigation. Quality unit is responsible for assuring investigation not necessarily conducting the investigation
IVA2	235	Please add in that the Quality Unit Manager should have the authority to detect problems and affect solutions.	
III G	272	It is recommended that there be a listing of the six quality systems rather than referring solely to the diagram. Also, suggest a link from the Six System Inspection Approach to the Quality System Model	While the document provides a good linkage from the regulations to the quality system model, there is no linkage between the model and the 6 systems. For example, the Quality System is linked to Management, Resource, and Evaluation Activities; Laboratory Controls Systems is linked to Management, Resources, and Evaluation Activities
IV	282	Please add in phrase in italics: This section describes a robust quality systems that if "designed", implemented and "operated properly" could provide.....	It is not enough to implement.
IV A	306	Please add in phrase in italics: in the design, implementation, "monitoring and continuous improvement" of the quality system.	Continuous improvement is an important aspect of quality systems.
IV A	311	Please add in phrase in italics: in the design, implementation, "monitoring and continuous improvement" of the quality system.	Continuous improvement is an important aspect of quality systems.
IV A 1	317	"Aligning quality plans with the manufacturers..." please delete the word "system"	Quality Planning is a process that is part of a quality system. A section on quality planning would be beneficial.
IV A 1	328	It should be noted a quality system need not be global to be effective. A single site can be successful	
	331	It is suggest that there be an inclusion of a formal mechanism between management and senior management in the form of a documented quality plan and quality systems review.	consistent with QSR requirements for Management responsibility (§ 820.20)

IV A 2	346	Please focus on individual system owners here rather than the Quality System.	The focus would be better placed on individual system owners here rather than the Quality System. The management team should own the Quality System not a single senior manager. There may need to be clarification that a Quality System is made up of a number of quality systems (deviations, complaints, training, etc.).
IV A 3	358	What is stated in this document as being included in a quality system is really more what should be included in the SOP. A quality system should contain elements discussed before: defined inputs, outs, controls, value added steps, metrics. The addition of a flow chart would be beneficial.	
IV A. 3	367	Change word from "directives" to "management"	It is unclear as to which directives FDA is referring to. Management makes better sense. If this is incorrect, please clarify.
IVA4	391	Please clarify that objectives should be quality objectives for the site and should be placed within the quality plan.	It is preferable not to review personal objectives as some elements could be outside of the agency's inspectional authority.
IV A 4	395	Please add quality planning can be integrated with the overall plant planning process. There must be sufficient time devoted to the Quality aspects or there should be a separate process integrated as an input to the plant planning process.	This achieves the holistic approach to quality discussed in the introductory sections.
IV A .4	395	This establishes quality planning as a formal documented system. It needs to be clear which elements of quality planning can be subjected to FDA inspections and which are considered internal audit documents.	For a quality planning system to be effective, parts will be outside of inspectional jurisdiction.
	395	Change "identify resources" to "allocate resources"	In order to have an effective quality system, resources must be allocated not just identified
IV A 5	404	Please add in the phrase in italics: ..conduct reviews of the "performance of the quality system.."	It should be made clear that the performance in terms of data from metric should be considered rather than just a review of the design.
	405	Please add the phrase in italics: typically includes both an assessment of the product "and process" as well as the customer needs.	This acknowledges that quality systems should address the process not just the product meeting specifications
IVA5	415	It is unclear how this will be measured. This bullet point should be deleted unless there can be guidance as to clear measurement techniques.	
	417	Please add in a review of quality system indicators such as complaints, deviations, changes, and Annual Product Reviews	A comprehensive review of these indicators assure continuous improvement and communication of the systemic issues to senior management
	419	Please add the phrase in italics: Outside of scheduled reviews, the "key indicators of" the quality systems are typically included as a standing agenda item in general management meetings.	A review of specific items as part of the quality system is imperative for communication and specific areas of improvement

IVA5	428	It will need to be clarified that these recorded results of the management review are considered internal audit documentation	For a quality planning system to be effective, parts will be outside of inspectional jurisdiction.
IVB1	447	Suggest deletion of the word "sufficient"	It is unclear how "sufficient allocation" of resources will be measured.
IV B 1	449	Please include a role for all employees instead of a defined role only specified for senior management.	Under a quality system employees should also be expected to play an active role in monitoring and controlling the systems/processes they work with.
IV B	455	Warehousing should be included as an additional bullet point.	The guidance only discusses the acquisition and receipt of materials. The proper shipping, storage, and warehousing of materials and products should be included in the scope of this guidance.
IV B	456	There should be a bullet added for resources to operate the quality system.	This is consistent with the concept of resource allocation.
IV B. 2	462	Change "cross-cutting" for "cross-functional"	More conventional and clearer terminology
IV B 2	474	Please separate the training element of a quality system as its own section.	Training is an integral part of every quality and manufacturing system.
	487	Please add in the phrase in italics: Evaluation of effectiveness of training "to assure learning or knowledge transfer has occurred"	This addition helps to define the purpose of the evaluation
IV B 3	499	Please revise the mention of FDA reviewing facilities. Instead, it would be better to have more discussion of design for purpose, validation/qualification, calibration, operation, maintenance, control of facilities, and the role that product and engineering play in this area.	
	515	A quality agreement is more applicable to a contract manufacturing arrangement. A contractor should be covered under a service agreement. Consultants should be managed as described in CFR 211.34	Currently quality agreements are necessary for contract manufacturing relationships. Records of consultants including the nature of the work performed and the consultant's competencies to perform their activities are kept.
IVB4	523	It is unclear whether the agency will allow a contractor to be authorized to release final product	If contractor has good quality systems as determined by audit, history, etc., the contract giver should be able to delegate the authority to release product.
IV C 1	545	Suggest adding in technology transfer from R&D to production as a quality system.	
IV C	558	Expand from "validation activities" to "process control activities"	Validation is too limiting a concept.
	559	Change from "effects" to "interaction of"	Interaction is a broader concept

IV C 2	569	It is unclear if this is applicable only to packaging and labeling or to all manufacturing operations. Labeling should be discussed as a system, including its general inputs and outputs, and the critical interfaces to other systems.	This will then serve as an example for other systems not covered in this guidance.
IV C.2	589	Please add the phrase <i>in italics</i> : Change controls should be maintained throughout the design of the "commercial packaging" process.	To reinforce change management is a continuum throughout the life of the product
IV C 3	593	Inputs should not be used in a narrow way to define raw materials. This will only serve to confuse a general term with an area where we already have the term raw material.	
IV C 4	628	Include change management as a separate quality system not as a paragraph under manufacturing processes.	Change management should be one of the quality systems reviewed in this paper not included as a paragraph in the section on manufacturing process.
IV C. 3	628	Change "recommended" to "shall" and rearrange sentence	Use of the word "recommended" implies that it may not be necessary to apply change management in the examples given. However to assure appropriate control change control must be employed in these instances
IV C 4	634	Please state that "Perform and monitor operations" is not a quality system but a manufacturing system.	In this case monitoring of operations is only one part of running a quality and compliant manufacturing system. What are the other parts? Inputs, outputs, value added steps, controls, metrics?
IV C 3	636	Delete the first sentence: "Core purpose of implementing a quality systems approach is not to enable a manufacturer to more efficiently and effectively perform and monitor operations."	The core purpose is to produce a product that meets all requirements in an effective and efficient manner
IV C 4	644	Please add in the potential role of PAT.	
	646	Change from "process weakness" to areas of "higher risk"	The concept of higher risk is consistent with this document
	651	Change "validate" to "assure conformance"	Assure consistency with PAT guidelines
	666	Change "change control" to "change management"	Please refer to Item B in our cover letter.
4	689	Please delete paragraph on using process data to improve manufacturing control.	The idea of static process parameters – that should always be meet – is not consistent with process control.
	708	Change "change control" to "change management"	The term change management contains the concept of inter-relatedness of process, specification, software changes in a multi-disciplinary approach.
IV C 4	725	Please add in phrase <i>in italics</i> : if implemented "and operated well, will...."	It is necessary for the quality systems to be operated well for the statement to be correct.
	730	Delete word "statistically" from "invalidation of test results should be scientifically and statistically sound and justified."	Statistics should not be used to justify invalidation of a test result. This additional requirement is not consistent with other draft guidances and should be removed.
	734	Please add in the phrase <i>in italics</i> : ..the manufacturer should consider shipment "and storage" requirements...	Storage of pharmaceutical products can impact the quality of the products.

IV.C. 4	737	Change "continually" to "periodically" when referring to trends. Alternatively, it can be said that data should be continually monitored for trends.	A certain amount of data is needed to identify a trend. The data must be collected over a period of time and it is best established through continuous monitoring
IV C 4	741	Please include that ongoing process capability measurements can provide knowledge that a process is still in a validated state.	
IV C 5	767	Please define the "proper authorization"	It is necessary to clarify if it is an external or internal authority.
IV C. 5	769	Change the term "can" to "should" or "must" or insert language such as "a recall should be considered"	Pfizer is not aware of an option not to recall a product that does not meet specifications unless firm has data that demonstrates the deviation is insignificant – in such cases a revision of the specification should be considered
5	770	Change "Customer complaints should..." to "Quality related customer complaints should be handled as potential discrepancies..."	
IV D 1	790	"Analysis of data can provide" suggest "Analysis of data can provide an indication of the state of control of a process."	
IV D.1	794	Trending on a regular basis (more than just annually) may not be possible for low volume product. Intervals need to be based on lot /product volumes	Data in these cases is insufficient to detect significant trend
IVD2	808	An annual audit of entire quality system may not be achievable.	It is logistically impossible and not value added to audit the entire quality systems. Elements of the system and the effectiveness of the quality system should be reviewed annually.
IV D	824	Please add in the phrase in italics: Understanding of quality issues "and their risk to patients"	Addition of risk to patients is consistent with a risk based model for GMPS
IV D 4	840	Please change from "Corrective Action" to "Preventive Action"	This section describes Preventive actions not corrective actions.
V	890	Remove delete sentence " Quality professionals are aware that good intentions alone.."	This sentence is not value added.
	895	Please add in a summary bullet describing change management.	Change management is an essential function of a quality system and is discussed in detail