



GlaxoSmithKline

December 2, 2004

Management Dockets, N/A  
Dockets Management Branch  
Food and Drug Administration  
HFA-305  
5630 Fishers Lane, Rm 1061  
Rockville, MD 20852

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**Re: Docket Number 2004D-0443  
Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good  
Manufacturing Practice Regulations**

Dear Madam or Sir:

Enclosed please find comments from GlaxoSmithKline, including general and specific comments for the Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. These comments are presented for consideration by the FDA. The general comments are presented first, with the specific comments with suggested text presented in order by line number in the draft guidance.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting the comments for this draft guidance by hardcopy. Therefore, you will receive this letter with two copies of comments.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S. Whisler, Ph.D.  
Assistant Director  
New Submissions, North America

2004D-0443

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## General Comments

The following general comments are provided by GSK as supportive of the ideas/statements presented in the draft guidance.

- The positive approach presented in this document by FDA to apply modern quality management and risk management techniques to update the way pharmaceutical manufacturing and product quality is regulated and to bridge the gap between the 1978 regulations and current quality management concepts is commended.
- The intention of the document is clearly stated on page 1 as a guidance document with the use of “should” throughout indicating a suggestion and not a mandated requirement.
- Very progressive and pragmatic goals for the guidance indicate that if a manufacturer has good science based understanding of the processes and effectively applies the quality management concepts in this document then that manufacturer should be able to implement improvement changes without prior regulatory filing.
- Good management practice and effective leadership have been recognized as key enablers to an effective quality system.
- The underlying philosophy to the guidance that quality needs to be built into the product is good; the importance of applying quality by design principles throughout a product’s lifecycle is a strong message that appears throughout the document.
- The document is clearly scoped for human and veterinary pharmaceutical drugs and biological drug products and will provide a uniform quality management approach across these classes of products. It is good to see the approach that has been taken in harmonizing the guidance document content with other well recognized and proven quality systems such as the QSIT Guide for medical devices and the ISO 9001 and 9004:2000 standards.

The following comments provide suggestions for improvement on those ideas/statements presented in the guidance that we consider as less positive.

- This is just one of several initiatives that has been developed under the banner of Pharmaceutical CGMPs for the 21<sup>st</sup> Century. It would be useful to provide a simple summary of the objectives of the different documents and the interrelationships between them and other existing documents including the Guide to Systems Based Inspections. This would help users and customers of the documents understand the context and when, how and by whom each should be applied.
- There are statements throughout the document that refer to non alignment/differences of the content with existing FDA regulations and other guidance documents i.e. CGMPs and Guide to Systems Based Inspection. This is sending some negative messages and may cause confusion in interpretation by the users. Positioning and clarification is required on if and how all of these documents will be brought into alignment in the longer term.
- Figure 1 on page 7 that attempts to integrate the Quality System with the five manufacturing systems (and not treat them as discrete entities) does not convey this intended message very well. What, if any, aspects of the five manufacturing systems would actually fall outside the scope of the Quality System?
- The value of applying and reviewing quality measures/performance indicators is not stressed in the document. Quality measures and the associated management review of the metrics should be included as a specific item.
- There is a lot of reference to quality throughout the Product Lifecycle. The need to manage quality throughout the supply chain should also be stressed; for example there is currently limited recognition or reference to the importance of control of product shipment/distribution.
- Product release is regarded as a key quality process in the EU but it receives little if any reference within this guidance document.

And finally, the following question is posed.

- Has each and every 21 CFR CGMP regulation been addressed by this proposed Quality Systems Approach? Has anyone checked this?

## Specific Comments

The following specific comments are provided with the line number and proposed change.

Line Number	Comment	Proposed Change
282-291	This paragraph appears to be a reiteration of what has already been stated in II. B. Goal of The Guidance and in II. D. Organization of this Draft Guidance.	Paragraph could be deleted unless consensus is that there is value in restating the goals etc.
366-367	Clarification is required on what is meant by "change requests to directives". Is directive meant to relate to the policy content of the quality system?	Alternative wording is suggested as "--- submit request for changes to the content of quality system documents".
368	The sentence "It is also recommended that, when operating..." needs editing to remove the word "record".	Remove the "record" that comes immediately after "document".
417	There is no mention of review of performance indicators.	Reword bullet to read "Quality performance indicators including product quality performance metrics".
518	The use of the terms "contract firm" and "contracting manufacturer" is confusing.	Suggest the use of contract giver and contract acceptor would provide more clarity.
660	What is meant by an activity that "continues"? This needs to be qualified as the question that springs to mind is for how long?	Suggest "continues" is qualified with "throughout the product lifecycle".
679	The previous sentence is about completing batch production records. The next sentence talks about time limits. Clarification is required on time limits for what?	Amend wording of sentence to clarify the context and that it is "time limits for processing".
702	The bullet "Are collection methods documented" needs clarification.	Add "data" before "collection methods".
750	The phrase "(e.g. specified control parameters strength)" is not clear.	It would make more sense if "strength" were removed.
762	Unclear what is meant by product availability. Is it bioavailability or availability to the consumer? Either way efficacy should also be referenced?	Efficacy should be included in the qualifiers to "product".
767	"With proper authorization" occurs twice in the sentence.	Remove the second "proper authorization" and amend wording so that this part of the sentence now reads "or, with proper, documented authorization, either allowing the product to proceed or using the product for another application".

(Continued)

### Specific Comments (Continued)

The following specific comments are provided with the line number and proposed change.

Line Number	Comment	Proposed Change
821	The section is titled "Risk Assessment" but the content of the section is broader than just assessment because it includes risk mitigation, etc.	The suggestion to retitle the section as "Risk Management" to reflect the scope of the content.
832	The word "reiterative" implies that you would be just assessing the same risks again and again.	Replace the word "reiterative" with "iterative".
852	In order to determine corrective actions you need to understand the real or most probable cause of the problem.	"Root cause analysis" should be added as an additional bullet to the list of information sources
871	This section "Promote Improvement" is weak and needs more concrete suggestions for supportive activities.	Consider the inclusion of activities such as employee suggestion schemes, benchmarking, and self-assessment against business excellence models in this section (see following text for section suggestion).

#### Suggested Text for Section IV. D. 6. Promote Improvement (lines 871-880)

##### Promote Improvement

A key underlying purpose of the quality management system is to continually drive improvement. Implementing the quality activities in this model should promote improvements in the effectiveness and efficiency of the business processes and of the quality system itself.

Improvement plans and programs should be derived from observations and recommendations arising from

- Trend analysis
- Audit and self assessment
- Corrective and Preventive Actions
- Risk Management
- Management Review

Other sources of improvement could be from lessons learned from incidents and from the knowledge and experience of people in the organization.

Prior to implementation, improvement actions should be assessed for the need for change control.

Managers should create a culture of improvement where people are encouraged to contribute improvement suggestions and to participate in ongoing improvement activities. Setting improvement objectives as part of the quality planning process, ensuring managers actively participate in a coordinated program of system reviews, operating suggestion schemes, and recognizing and rewarding improvement achievements are all activities that will aid the establishment of a culture of improvement.

Managers should benchmark the quality improvement practices of other organizations with the aim of improving their own internal practices.