



**ABBOTT LABORATORIES**  
**Corporate Regulatory and Quality Science**

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

**Ref: Docket No 2004D-0443 – Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**

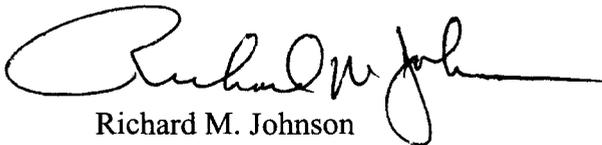
To Whom it May Concern:

Abbott Laboratories is very pleased to have the opportunity to provide comments on the Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations published on October 4, 2004 in the *Federal Register*.

We participated in the development of the comments submitted by PhRMA and PDA and our comments reflect that effort.

We thank the Food and Drug Administration for your consideration of our comments. Should you have any questions, please contact Kathy Wessberg (tel: 847-938-1264, e-mail: kathy.wessberg@abbott.com).

Sincerely,



Richard M. Johnson

Encl: Comments

2004D-0443

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## ABBOTT LABORATORIES COMMENTS TO FDA ON

Docket No. 2004D-0443

### COMMENTS

#### General Comments:

##### **Glossary/Definitions/Vocabulary**

Some terms/phrases are not defined, and without definition they may be open to differing interpretations. (see specific comments for details). In addition, the term "Modern" is used extensively in the Guidance. It is not clear what the word means. Finally, terminology is not consistent throughout the document. For example use of the words managers, management, officers, & senior management.

##### **Impact on Regulatory Systems**

It is unclear how the modern Quality System will impact the current regulatory submission requirements. The regulatory system to accommodate improvement still needs to be defined.

##### **Harmonization of Guidances/Requirements**

This document is linked to the proposed ICH document referred to as Q10. Since the conceptual areas to be covered in Q10 are covered in this document, it would be beneficial to both regulators and industry if a common international agreement could be reached in a single document.

It is important that we harmonize the cGMPs to the extent possible with other widely used quality management systems including ISO 9000, QSR, and International Pharmaceutical regulations.

##### **Quality by Design (Design Control)**

This guidance emphasizes Design Control. There is currently no guideline on Quality by Design for pharmaceuticals, and no 21 CFR 211 requirement for Design Control. Will this be treated as an inspectional expectation?

##### **Disconnects/Document Clarity**

The document flow is sometimes difficult to follow. Some sections have extreme detail (management review) while others are less specific in this document. The structure does not appear to parallel existing regulation or guidance.

The intent of the footnotes is at times confusing and unclear. CFR citations don't match up well or are loosely interpreted from the regulations (see specific comments).

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**Implementation**

It is recommended that the FDA hold Forums and/or Workshops on how they intend to implement this document and how they will be evaluating implementation of this document.

Significant time will be needed in order to implement this guidance.

**Specific Comments:**

<b>Line # (s)</b>	<b>Guidance Text</b>	<b>Comments</b>
24-25	"...Is not intended to place new expectations on manufacturers"	All manufacturers do not practice many of the specific recommendations in the guidance. This will become problematic if investigators use the guidance as a cGMP requirement during inspections.
45-46	Many pharmaceutical manufacturers are implementing comprehensive, modern quality systems and risk management approaches	Change sentence to: Many pharmaceutical manufacturers are implementing comprehensive quality systems and are initiating risk management approaches.  Delete the word "modern".
71-73	The guidance describes a comprehensive quality systems model, which, if implemented, will allow manufacturers to operate robust, modern quality systems that are fully compliant with CGMP regulations.	Document infers that a manufacturer will be in full compliance if a manufacturer operates their quality systems according to the guidance. This statement is a broad generalization since many requirements are not defined nor referenced in this document. For example, validation, process design, etc.  Delete the word "modern".

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Line # (s)	Guidance Text	Comments
98-102	The FDA has concluded that modern quality systems, when coupled with manufacturing process and product knowledge, can handle many types of changes...without the need for regulatory submission. Manufacturers with appropriate process knowledge and a robust quality system should be able to implement many types of improvements without the need for a prior regulatory filing	<p>This is a key point which industry agrees with, however the regulatory system to accommodate improvement still needs to be defined. Need detail on the mechanism for reporting. Does this mean these changes can be reported in annual report rather than CBE-30 or prior approval or that no information is provided but rather maintained locally.</p> <p>In addition, it is not clear how the phrases “appropriate knowledge and robust quality systems” are defined.</p> <p>Delete the word “modern”.</p>
115-116	It may also be useful to manufacturers of components used in the manufacture of these products	It is not clear if the scope of this document applies to component manufacturers (suppliers). Delete this sentence. Section IV.C.3 (line #s 591-632), Examine Inputs, describes the requirements for raw material control.
190	...manufacturing changes (e.g., changes that alter specifications, a critical product attribute or...	Critical product attribute is not defined in the documents glossary. Add definition to Glossary
196-197	Manufacturer is empowered to make changes based on variability of materials used in manufacturing...	Further clarity is needed. Need more detail on how a manufacturer can make changes and what is meant by variability of materials
251	Compliance program is to be able to assess whether each of the systems is in a state of control.	It is not clear what is meant by desired state of control. Desired state of control is not defined in glossary.
290-291	FDA regulatory and inspectional coverage will remain focused on specific CGMP regulations.	Since this document represents the Agency’s current thinking, the concern is investigators will begin to cite companies for not complying with specific requirements contained within because this will be interpreted to be current CGMP.
319-320	Senior managers set implementation priorities and develop action plans.	Delete “senior”. Implementation priorities and action plans are set at various levels of the organization, not only at the senior level.
324	Advocating continual improvement of operations and the quality system.	Add “where appropriate”. Continuous improvement should not be applied to everything, but should be based on need, risk, etc.

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327-329	In a robust quality systems environment, managers should demonstrate strong and visible support for the quality system and ensure its global implementation throughout the organization (e.g., across multiple sites)	<p>Change to “In a robust quality systems environment, managers should demonstrate strong and visible support for the quality system. Management should have an understanding of applicable international regulations and apply that knowledge to ensure appropriate global implementation of their quality system throughout the organization (e.g., across multiple sites).”</p> <p>Document refers to global implementation throughout the organization. Many companies are highly diverse organizations and implementing the same quality system may not make sense due to differing regulations or foreign requirements.</p>
340-341	Senior managers have the responsibility to ensure that the organization’s structure be documented.	Delete “Senior”. This is a management responsibility but may not always be a “senior” management responsibility.
357-358	...design and implement provides clear organizational guidance and facilitates systematic evaluation of issues.	Replace “design and implement” to “review and approve”. Senior management may not directly design and implement.
363	The manufacturer’s policies to implement the quality systems criteria, and the..	Change “policies” to “requirements”. The requirements may not always be in the form of a policy.
368	Under a quality system, manufacturers develop and document record control procedures to complete...	Delete the word “record”. This is redundant with the same word that follows later in the sentence.
370	Quality system activities.	Change “activities” to requirements. The word activities is very vague and implies documentation for items that may not be necessary.
378-379	Under a modern quality system, policies, objectives, and plans provide the means by which senior managers articulate their vision of quality to all levels of the organization.	Change “vision of quality”... to quality requirements and direction”. Vision is too futuristic and implies desired state. Although that may be communicated, the primary role of the policies, plans, and objectives is to specify the requirements and direction. Delete “modern”.
385-386	It must be communicated to, ...personnel and contractors (as applicable), and revised as needed.	Change ‘personnel’ to “employees”.

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389-393	Senior management is expected to ensure that the quality objectives are created at the top level of the organization (and other levels as needed) through a formal quality process. Objectives are typically aligned with strategic plans. A quality system seeks to ensure that managers support the objectives with necessary resources and have measurable goals that are monitored regularly.	This section indicates that goals should be published and communicated to operational level employees, with a direct link to the corporation's strategic objectives. Although goals/objectives are used in most companies, they are not part of the inspection process and they may encompass areas outside of the quality system. Does the Agency expect to change this approach and review these goals/objectives as part of the inspection process?
403-404	Under a quality system, senior managers are expected to conduct reviews of the whole quality system according to a planned schedule.	Change "senior managers are" to "management is". Management review is not only a function at the senior level. Delete the word "whole". The management review may not need to review all areas of the quality system. The review should be flexible enough to focus on those areas necessary.
405-406	Such a review typically includes both an assessment of the product as well as customer needs (in this section customer is defined as the recipient of the product and the product is goods or services being provided).	Change customer needs to "customer feedback". A review of customer needs may imply that a proactive effort is required on behalf of the manufacturer to resurvey customers for their feedback.
407-417	Under a quality system, the review should consider at least the following: (eight items listed)	Delete this section.
411	Customer feedback, including complaints	Does this mean all customers? Change to Formal customer complaints and feedback.
422	Review outcomes typically include:	Change the word "typically" to "may". Outcomes of management review may vary and typically suggests the points listed usually occur.
474	Under a quality system, continued training is critical...	It is not clear what continual training means. Define.
489-490	...it is important that supervisory managers ensure that skills gained from training be incorporated into day-to-day performance	Delete the word "supervisory". Referring to managers is sufficient since the term "supervisory managers" is not used elsewhere in the document.  Change to "it is important that managers ensure that re-training is administered at appropriate intervals to ensure that employees skill sets remain current for their job functions".

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494-495	...and manufacturing processes related to the product, are responsible for specific facility and equipment requirements.	Add "are responsible for defining specific facility and equipment requirements. Clarification is needed since the technical experts may not be responsible for meeting the requirements; this may be the responsibility of manufacturing, etc.
505-507	The CGMP regulations place as much emphasis on process equipment as on testing equipment (211.42 (b))	Delete sentence. Facilities and equipment reference 211.42 (b) in the paragraph on qualification, calibration, etc. of equipment; 211.42 is about adequate building space. Subpart D beginning at 211.63 is about equipment.
514-516	Quality systems calls for contracts (quality agreements) that clearly describe the materials or service, quality specifications responsibilities, and communication mechanisms.	Need to clarify the term "services". It will be important to make sure that a company would have sufficient time to implement this requirement since most companies have a wide variety of services that do not have quality agreements. The proposed guidance would be more obtainable if it defined specifically, those outsourced operations that required a quality agreement and those that would be exempt from such a requirement. For instance, contract services that are accredited by regulatory bodies such as NIST or USP.
520-21	...and the contract firm's and contacting manufacturer's quality standards should not conflict.	Remove this statement. A more appropriate requirement would be, "Sufficient detail shall be provided in the Contract (Quality Agreement) as is necessary to ensure that compliance with all applicable regulations is integrated between the two firms". It is unreasonable to assume that the contract manufacturers quality standard will be identical to every standard of their contract firms.
521-522	It is critical in a quality system to ensure that the contracting manufacturer's officers are familiar with the specific requirements of the contracts.	Change officers to "management". Keeps terminology consistent within the document. Need to clarify what familiar means.

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Line # (s)	Guidance Text	Comments
548	Documenting associated processes will ensure that critical variables are identified.	Change to Documenting associated processes "and changes to these processes" will ensure... To clarify that documentation of the process changes are as important as the documentation of the original process. How and where should the design process be documented? What is the requirement for design history? Sufficient time will be required to comply with this requirement as proposed. Formal documentation and approval of the design control process for pharmaceutical products is not standard practice.
549	This documentation includes:	Change to This documentation "may" include... Since processes and changes vary not all of the items listed may apply.
577-579	Distinct labels with discriminating features for different products..., should be included to prevent mislabeling and resulting recalls.	Provide examples or a definition of "discriminating features". Is the requirement necessary if there are other sophisticated control mechanisms in place to prevent label mix-ups, such as bar coding and on line vision systems? Mix-ups in the field are not addressed in the guidance.
581-589		This paragraph seems to be out of place. It appears to be a summary on design. Should go in line 542 – Design & Develop Product and Processes.
600-601	The quality systems model calls for the verification of the components and services provided by suppliers and contractors.	Request clarification, since CGMP specifies contractors and consultants and the proposed draft addresses contractors only. Are consultants exempt from these requirements? A definition of "consultant" would clarify this requirement.
608-609	Sufficient initial tests must be done to establish reliability and to determine a schedule for periodic rechecking.	Need to further clarify what sufficient initial tests means. Also how detailed and how often does periodic retesting have to be?
613	The quality systems approach also calls for the auditing of suppliers on a periodic basis. During the audit, the manufacturer can observe the testing or examinations...	Periodic basis needs further clarification. The use of the term "observe" implies that the audit is an <i>on site</i> inspection of the supplier. We recommend harmonizing the term, "audit" with that of, "quality audit" as defined in 21CFR 820.3(t).

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651-652	...from development to commercial production, a manufacturer should be able to validate the manufacturing process.	With the concepts of continuous verification through the use of PAT applications, process validation may not be necessary. Suggest "...a manufacturer should be able to ensure the process is in control through continuous verification or process validation".
658	The entire life cycle should be addressed...	Change to "product life cycle". Consistency in vocabulary. Line 703 refers to product life cycle
659-660	Thus, in accordance with the quality systems approach, process validation is not a one-time event, but an activity that continues.	Need more clarity on the expectations on what is necessary to demonstrate that a process is validated. There is no description for continuous validation. What data would be needed to show validation is still OK? When would revalidation be necessary? If so, what are the requirements? After any changes or after a specific period of time?
674-675	Both the CGMP regulations and quality systems models calls for the monitoring of critical process parameters	A definition of "critical process parameters" (CPP) is required. Also the requirement appears to state that all CPPs need to be monitored during production. Would it be acceptable to monitor selected CPPs that have been validated to demonstrate that the system is under control?
677	Process steps should be verified using a validated computer system or a second person.	Add "Critical" process steps...Not all process steps may need to be verified since many steps may not be critical.
689-690	...manufacturing processes must consistently meet their parameters.	Add their "critical process" parameters. Since not all parameters may be critical, it is important to keep the focus on those identified as critical.
730	Invalidation of test results should be scientifically and statistically...	Define invalidation of test results.