

# Facility Automation Information Management (FAME) Systems

Tuesday, 18 January 2005

Documents Management Branch [HFA-305]  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

**RE: Docket No. 2004D-0443**

## FORMAL COMMENTS ON:

**Docket Number:** 2004D-0443

**Comments On :** "Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations"

Pursuant to a "request for comments" promulgated in *FEDERAL REGISTER*, 69(191), page 59256, Monday, 4 October 2004

## BACKGROUND

On 15 November 2003, **FAME Systems** provided comments to this docket based on an in-depth reading of the FDA's "**Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations** [G:\6452dft.doc 9/28/04]."

That review added elements that more soundly connected various issues in the Draft provided by the Agency to current good manufacturing practice (CGMP), in general, and the drug CGMP and other regulations with which the Agency's draft guidance is required to be congruent.

To complete the comment process, **FAME Systems**:

- ❖ Has reviewed the formal comments, *other than those submitted by FAME Systems*, available electronically in Public Docket 2004D-0443 as of 9 January 2005.
- ❖ Is now submitting **FAME Systems'** scientific and CGMP-conformance assessment of those formal comments to the Docket for review by the Agency and the public.

To clearly separate **FAME Systems'** review statements from the formal comments of those who submitted such, the review comments are in an **Arial** or **italicized Arial** font and the original commenters' submissions are in a **Times New Roman** or the other fonts used by the commenters.

In general, the available formal comments were reviewed in the order they were posted to the docket and then, within each posting date, by the Agency's posting category for the categories, "C," "EC" or "EMC."

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For simplicity, each commenting firm or group will be addressed in the singular even when the comments are clearly from multiple persons.

Further, when either a binding regulation or a statute is quoted, the text is in a **Lydian** font.

When other recognized sources are quoted, a **Perpetua** font is used.

Should anyone who reads this reviewer's commentary find that its review statements are at odds with sound inspection science or the applicable CGMP regulations, or that additional clarification is needed in a given area, then, *in addition to providing the sound science or rationale that refutes the review text provided or his or her clarifying comments to the public docket or the Agency*, he or she is asked to e-mail **drking@dr-king.com** a copy of that sound science, rationale, and/or commentary.

Respectfully submitted,

*Dr. King*

Paul G. King, Ph.D.  
Analytical Chemist  
**FAME Systems**

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**C-01 Comments By Lloyd's Register Serentec, Inc., Posted 12 November 2004**

Serentec begins by stating:

"We as a company agree with and commend FDA on this draft guidance, and are impressed with the direction the agency is taking toward harmonizing GMPs (sic) with modern quality systems, resulting in standardization of quality management principles."

Serentec's reviewed comments are as follows:

"In line 71 of the guidance, you state, 'This guidance describes a comprehensive quality system model...' To meet the definition of the word 'comprehensive,' a quality system should be all-inclusive, encompassing a key element that is present in all modern, robust quality systems: independent, third party audit and certification. Many other industries (e.g. automotive, aerospace, electronics and food) have embraced the concept of third party independent audit and certification to a particular standard such as ISO9001 as part of their comprehensive quality systems.

To best convey FDA's desire to harmonize GMPs (sic) with these modern quality systems, we would like to suggest that you include the concept of third party audit and certification under 'Evaluation Activities' in the final guidance.

A certified quality system clearly shows a commitment by the manufacturer to produce reliable, quality products, creating confidence and enhancing its reputation in the marketplace. FDA has already moved in this direction successfully in the medical device industry, starting with Class 1 devices and now extending to Class 2 that go through third party certification.

Some of the specific benefits of third party audit and certification to FDA and industry are:

- Standardizing quality management principles
- Giving companies a tangible method to measure and substantiate their claim that they have a quality management system in place
- Providing FDA with another tool other than their own resources to ensure quality

We believe the inclusion of third party audit and certification in the final guidance will serve to further the goals of the FDA in the area of quality improvement in the pharmaceutical manufacturing industry, and give manufacturers a method of substantiating their implementations of quality systems."

This reviewer has no problem with this commenter's proposal other than to note that having a well-defined quality system that is third-party audited is no guarantee of the quality of the products produced.

*Unless such third-party auditors were required to continually demonstrate their understanding of and auditing not only to the minimums established in the quality system being audited but also with the minimums established in the applicable CGMP regulations as well as the third party's being audited for CGMP compliance, this reviewer supports the proposed third-party audits if, and only if, the Agency's audit scheduling were to ignore whether or not a third-party auditor is involved in the quality assessment of regulated firm.*

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This commenter has directly and indirectly reviewed the operations of Agency regulated facilities that purport to comply with a recognized quality standard that involves a third-party audit and found instances where the quality system in place did not translate into a better quality product or a CGMP-compliant operation.

Thus, while supportive of a firm's decision to become certified to some recognized generic quality system standard, this reviewer knows, *from both personal experience and that shared by other auditors*, that the Agency should not permit such status or audits to: **a)** take the place of **or b)** influence the Agency's inspection of a given facility for compliance with all the CGMP regulations that are applicable to the operations of that facility.

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**EC-02 Comments By F. Hoffman-La Roche, Posted 12 November 2004**

Hoffmann-LaRoche begins by stating:

“We have only some minor comments on this document.”

Hoffmann-LaRoche's reviewed comments are as follows:

“Lines 167ff: We propose to reword this chapter according to the risk management terms used in the current ICH Q9 draft:

‘The concept risk management is a major focus of the Pharmaceutical CGMPs for the 21st Century Initiative. Quality risk management can guide the setting of specifications and critical process parameters. Risk assessment tools are used in determining the need for discrepancy investigations and corrective action. As risk assessment tools can be used more formally by manufacturers and authorities, it can be implemented within the quality system framework.’

Footnote 6

propose to reword as: ‘This concept is being developed under the ICH Q9 Quality Risk Management Expert Working Group.’”

Other than to note that the text in question starts at Line 169 in the “pdf” version of the draft and not Line 167, this reviewer sees no problems with the draft's text other than the original changes this reviewer proposed in comments to this Public Docket (**see** 04D-0443-emc00002-01.pdf).

Since this commenter provides no rationale for its view, this reviewer sees no need to comment further.

“Line 390-393: The requirement to use ‘a formal quality planning process’ as well as the requirement of ‘measurable goals that are monitored regularly’ exceeds the requirements described in § 211.22 (c-d), 211.100 (a) and could therefore conflict with the statement of lines 118-119.”

Again this reviewer notes that the text passages referenced in the “pdf” version of the draft apply to quality systems' expectations of top management and/or general quality systems and, not *per se*, to the quality control unit or the expectations of such embodied in the CGMP regulations for finished pharmaceuticals (21 C.F.R. Part 211)

Thus, this reviewer is at a loss to understand the basis of this commenter's taking exception to the recommendation (not requirement) for “a formal quality planning process.”

Moreover, this reviewer notes that “measurable goals that are monitored regularly” is a clear requirement (**see**, for example, 21 C.F.R. Sections 211.110, 211.165, and 211.180(e)) explicitly set forth in several contexts in said CGMP regulations.

Given the preceding realities, this reviewer finds that the commenter's concerns are clearly misplaced.

“Line 451-456: The resources for people of the Quality Units should be also mentioned.”

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This reviewer agrees for the most part with this commenter's statement and notes that the changes this reviewer proposed to this section of the draft in comments to this Public Docket ([see 04D-0443-emc00002-01.pdf](#)) seem to have addressed this commenter's current concern.

"Line 462-463: Sentence 'Management is also expected to develop cross-cutting groups to share ideas to improve procedures and processes' should be omitted. It describes too specifically only one way how the expectations could be achieved."

This reviewer disagrees with this commenter because, contrary to what the commenter states, the draft's text only states a clear expectation; it does not describe how that expectation is to be met.

Thus, this comment should simply be ignored.

"Line 487: Insert 'Periodic' in front of 'Evaluation of effectiveness of training'"

This reviewer sees no need to so restrict the "Evaluation of effectiveness of training" and notes that the most effective quality systems of which he is aware support the **continual** evaluation of the effectiveness of training.

Moreover, this reviewer finds that the term "Periodic" usually defaults to annual, or less frequent, evaluations of training that are, or over time tend to become, simply perfunctory exercises.

Finally, the implicit expectation of the CGMP regulations are that a complying firm must have up-to-date proof of the competency of all covered personnel.

Given the preceding realities, this reviewer is opposed to the change suggested by this commenter.

"Line 808: '...the need to periodically audit the system on a risk based approach.' The scope of the term 'entire' could lead to misinterpretation."

This reviewer finds the commenter has apparently misquoted the text in Line 808 – the draft actually states, "... the need to audit the entire system at least annually."

Since this commenter provides no rationale for the changes made to limit the audit (both in its scope and its nature), this reviewer, *understanding the true audit requirements that go hand in hand with a viable quality system*, emphatically objects to the revisions proposed by this commenter.

This commenter's failure to properly quote the text in question speaks to an apparently deep-seated aversion to a quality system approach that conforms to today's recognized standards.

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**C-02 Comments By Pfizer, Inc., Posted 30 November 2004**

Though the comments were correctly posted to Public Docket 2004D-0443, Pfizer incorrectly submitted its comments to an apparently non-existent docket, "Docket #2004-22206."

This reviewer thanks the FDA personnel who posted this comment to the proper docket.

That having been said, Pfizer begins by stating:

"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:"

Pfizer's reviewed comments are as follows:

**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."

This reviewer finds that this commenter's initial remarks seem to be, at best, a not so subtle attempt to distort the requirements of both a *quality-oriented quality management system* and the current CGMP regulations.

Factually, *even when a truly robust quality system is in place*, the manufacture of large collections (batches or lots) of product units still requires that appropriate statistical testing be done on an appropriate number of representative units having variable characteristics that must be ensured of being met. [Note: In that regard, the number required for batches of drug units of the size typically produced could validly be reduced from the need to test 200, or more, such representative drug-product units to the need to test only 40-some-odd units for each critical variable characteristic and the number of critical variable characteristics reduced from the current typical number of four (4) [typically, taken from the applicable uniformity characteristics such weight, content, drug release, impurity level, water content, deliverable volume, particulates, and preservative level and assay and sterility] to, in the most favorable cases only one (1) or, at most, two (2) critical variables.]

Thus, the commenter's second statement, though inexact, is factually correct.

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However, the commenter’s third statement, “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,” is at odds with the requirement minimums of the CGMP regulations as well as the requirement expectations of quality-oriented production systems, which operate under a valid quality system that recognizes the value of statistical process control.

Further, the commenter uses the term “quality systems” as if all quality systems ensure that the outcomes are quality directed when, *in fact*, all that a “quality system” requires is that: **a)** there be a clearly defined written system that a firm has implemented and **b)** the firm is continuously following that system.

Thus, a valid, but non-CGMP-compliant, quality system can consistently produce product that does not ensure that every unit produced will, *if tested*, meet its CGMP-required *minimums*.

In addition, it is not the possession of “process knowledge,” as this commenter states, but rather the application of *scientifically sound* and *appropriate* in-process controls that ensures that final product units will, if tested, meet all of their specifications.

In general, *only* the *results* obtained *from* appropriately evaluated *representative samples* of product units for each *critical characteristic* of the drug product can validly be used to “predict the above mentioned characteristics” (“identity, strength, purity, and other quality characteristics designed to assure the required levels of safety and effectiveness”) of each batch as required by both the applicable CGMP regulation *minimums* and quality manufacturing systems operating under statistical process control.

Thus, *without the requisite representative results required*, it is not possible for quality to progress “into a more probabilistic definition” because, as even every gambler knows, *without results that predict the odds*, one cannot validly predict the probability – one can only guess.

Therefore, the commenter’s statements here, “Quality then progresses into a more probabilistic definition” and “This will necessitate transitioning from compliance systems to quality systems” are, *at best*, devoid of any meaningful content.

However, this reviewer does fully agree with the validity of this commenter’s next statement, “For example, trending of data is identified as an important element of a good quality system”; but notes that process-step representative data are required to effectively implement such “trending.”

Finally, *given that each commenter speaks from the viewpoint of the systems that it currently uses*, the commenter’s next statement, “However, much of the data collected is for compliance systems and can not be meaningfully trended,” clearly indicates that this commenter’s “compliance systems” are not CGMP compliant because the CGMP minimums clearly require each regulated firm “to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product” for each batch or lot (21 CFR 211.110(a)).

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Since the requisite CGMP in-process evaluations require that the in-process and drug-product “samples shall be representative and properly identified” (21 C.F.R. Sections 211.160(b)(2) and (b)(3)), it is clear that today’s CGMP requires the evaluation of a statistically valid *representative samples* of each batch or lot both in-process and during the release procedures used by a CGMP-compliant firm.

Consequently, provided such firms comply with the applicable CGMP minimums for finished pharmaceuticals, the data collected for such firm’s “compliance systems” is easily trended.

Thus, this commenter’s statement that their “data collected is” for their “compliance systems” and cannot “be meaningfully trended,” is a clear admission on the part of this commenter that this commenter knows that its “compliance systems” do not meet the clear CGMP minimums established in 21 C.F.R. Part 211 – a fact that this reviewer hopes is effectively “noticed” by the Agency.

Overall, this reviewer finds little substance in this commenter’s remarks in the commenter’s “Item A.”

**“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.

This reviewer has no problem with the commenter’s remarks and could support the use of the more general term, “Change Management,” over “Change Control.”

However, as this reviewer pointed out in the comments he submitted to this docket, in reality all of the actions fall within the purview of the “Maintenance Qualification” (MQ) phase of the ongoing validation journey for each production process that begins in “Design/development Qualification” (DQ) and progresses to the MQ phase after the validity of fully function process has been established by a successful *initial* “Performance Qualification” (PQ) also less commonly, but more appropriately, labeled as the “Evaluation Qualification” (EQ) stage in validation.

Hopefully, those reviewing this commenter’s remarks and those of this reviewer will revisit this portion of the draft and generalize it into guidance that considers this section from the viewpoint of “Maintenance Qualification” as they should.

**“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

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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.”

This reviewer fails to see the point of this commenter's, at best, obtuse remarks here and would suggest that the Agency would be best served by simply ignoring them here, for the time being, as the commenter's closing statement suggests.

**“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.”

Since the draft is clear that it may be useful for all “manufacturers of components,” this reviewer sees no need to specifically address the taking “advantage of the regulatory flexibility discussed in lines 98 through 103” or to state that the “implementation of this guidance should be optional” because it is clear, *in the first instance*, that the guidance may be broadly used for components and, *in the second instance*, the implementation of all guidances is obviously optional in all cases.

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

Two of the key achievements of the FDA GMP (sic) 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 (sic). 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.”

First of all, this reviewer knows of no “FDA GMP (sic) Initiative;” since all of the FDA “CGMP” initiatives must, of necessity, be CGMP initiatives. [Note: In this reviewer's wide-ranging experience, this reviewer has found that those who mischaracterize “CGMP” as “GMP” (sic) either:

1. Lack the requisite training, experience and/or combination of both with respect to “current good manufacturing practice” (as that term is used in 21 U.S.C. 351(a)(2)(B)) which is properly abbreviated “CGMP, and the CGMP regulations appertaining thereto, or
2. Are consciously or subconsciously opposed to conformance to the minimums established in the CGMP regulations and/or the principles set forth in those sections of Titles 21 and 42 of the U.S.C. as the apply to the manufacture of safe and efficacious drugs meeting CGMP.]

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That having been said, this reviewer has no problems with the commenter's recommending that the "agency should give careful consideration to how to incorporate risk management and other optional practices into the pharmaceutical inspectorate curriculum," provided that consideration includes training in the auditing of quality systems in a manner that conforms to the recognized international standards appertaining thereto.

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**SPECIFIC COMMENTS**

<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
24, I	<p>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”.</p> <p>This reviewer does not agree with the commenter. He can only support the addition of the phrase, “and to continuously improve the quality” here; but sees no compelling need to add that phrase to the text.</p>	<p>Implementation of quality systems goes beyond fulfilling GMP (sic) requirements.</p> <p>Since, <i>contrary to the commenter’s implications</i>, the CGMP regulations provide a method for the compliance of a product with CGMP, the adoption of a “quality system” does not, <i>per se</i>, add any CGMP structuring beyond that already required in the CGMP regulations.</p>
47, II.A.	<p>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 that this is a valuable goal and supports an initiative to harmonize across other regulatory systems within the FDA and across other agencies.</p> <p>This reviewer cannot support Pfizer’s statement here because it is not limited as it should be to the pharmaceutical CGMP regulatory system.</p>	<p>The commenter provides no rationale for its remarks.</p> <p>Since this guidance is intended to address pharmaceutical CGMP regulatory systems, it is not appropriate to try to expand its scope beyond its stated areas of coverage.</p>
71, II.B.	<p>From the guidance: “This 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 (sic) 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.</p> <p>This reviewer both sees no such need.</p>	<p>FDA is defining what quality systems are needed but not what good quality systems are and how to implement quality systems.</p> <p>Since adhering to the minimum requirements of the current good manufacturing practice (CGMP) regulations defines the minimums for good quality systems and the purpose of FDA guidance is to outline what should be done without being overly prescriptive, this reviewer sees no need for any guidance, including this, to be overly prescriptive by providing guidance on “how to implement quality systems.”</p>
92, II.B	<p>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.</p> <p>This reviewer does not agree with the commenter’s remarks as, <i>within the limitations of the FDA’s mandate</i>, the current guidance has provided all the harmonization that is appropriate in this area.</p> <p>However, this reviewer does not object to the commenter’s addressing these remarks to the ICH members.</p>	<p>Harmonization of GMPs (sic), 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 and not an endpoint.</p> <p>Given the legal strictures imposed upon the FDA, the Agency should not attempt to exceed its authority or, <i>as it apparently has in some recent guidances impacting CGMP</i>, issue any guidance that conflicts with the clear minimum requirements of any binding regulation or statute.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
103,	<p>Please add 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”</p> <p>This reviewer does not agree with the commenter’s statement and suggests that it should be ignored. Further the “phrase in italics” is actually between quotation marks.</p>	<p>Please refer to Item C in the cover letter</p> <p>While the commenter’s phrase is artfully constructed, it misstates several realities:</p> <ol style="list-style-type: none"> <li>1. Firms adopt changes they do not enact them</li> <li>2. The US statutes and binding FDA regulations establish the limits on the allowable “regulatory flexibility” and not the quality system or how it is implemented.</li> </ol>
113, II C	<p>“...applies to manufacturers of drug products (finished pharmaceuticals) including products regulated...” Please revise to allow the application to Active Pharmaceutical ingredients</p> <p>Since the next sentence, “It may also be useful to manufacturers of components used in the manufacture of these products,” clearly addresses “Active Pharmaceutical ingredients” as the commenter’s general remarks state, the commenter’s remark here should be ignored.</p>	<p>Please refer to Item D in the cover letter</p> <p>Since the guidance already clearly allows this guidance to be applied to components, it allows the guidance provided to be adopted by those who manufacture an active pharmaceutical ingredient (API) or, for that matter, the manufacture of any other component that is used in the manufacturer of a drug product.</p>
118, II	<p>There will be a 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 (sic) deficiencies.</p> <p>This reviewer sees no such need for the implied FDA “inspectors” to need any training in quality systems as they are supposed to, and do, only audit for CGMP compliance which includes how well a manufacturer, processor or packer follows whatever systems that that firm has in place. Thus, <i>while this reviewer sees a need for training in representative sampling, statistics, the clear requirement minimums of the CGMP regulations, and compliance thereto</i>, this reviewer sees no need for training to “correctly assess quality systems” or to, <i>per se</i>, make “comments on quality systems.” However, based on the repeated misuse of the term “GMP,” this reviewer recommends that this commenter should carefully review its own CGMP training programs, as they are apparently deficient in this regard.</p>	<p>Please refer to Item E in the cover letter</p> <p>While this reviewer would support the training of FDA in the formal audit techniques appertaining to quality systems as they are universally applicable to the auditing of any entity for its compliance to the systems that it claims to follow, this reviewer sees no need for training in the assessing of quality systems <i>per se</i>. In this reviewer’s wide-ranging experience, the FDA training programs need to be beefed up in the critical areas that define CGMP compliance, including, but not limited to, <i>representative sampling and evaluation</i>, the difference between specific identity and USP Identification, the difference between purity and USP Assay, statistics (especially population statistics and the concepts of uncertainty, confidence, probability, and statistical quality control), and exactly what the clear strictures of the CGMP regulations for finished pharmaceuticals require for incoming, in-process, and finished product controls.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
146, III	<p>There is no definition of what constitutes a system. For example a system has system design, quality planning, inputs, outputs and a system owner.</p> <p>This reviewer agrees with the commenter’s observation, but notes that: <b>a)</b> it is up to each firm to define their own system <b>and b)</b> there are excellent recognized standards and texts that address this subject.</p> <p>Moreover, each firm should tailor its definition to the operations that make up its business.</p> <p>Thus, this reviewer would recommend that the Agency continue to leave the definition of what operations fall within a given firm’s quality system up to the manufacturer, processor, or packer who is implementing a quality systems’ approach to CGMP compliance.</p>	<p>In order to fully understand how to develop and implement quality systems, there is a need to be a basis understanding of a system.</p> <p>Since this guidance addresses a “<b>Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations,</b>” this guidance properly speaks to quality system “approach” issues and not “definition” issues.</p> <p>This approach is appropriate because there is a world of literature and standards that address what constitutes a “quality system” and how a firm can define its operations in a manner that defines a valid “quality system.” <i>Since the commenter wrongly suggests that this draft should address tangential issues,</i> this reviewer fails to see the value added by this commenter’s remark here.</p>
156, III A	<p>Please broaden definition of achieving quality to include concepts discussed in this document such as risk management.</p> <p>This reviewer is opposed to this commenter’s unsupportable request which discloses this commenter’s apparent ignorance of the fact that the CGMP regulations are themselves risk based and, <i>therefore,</i> provide the minimum that a CGMP-compliant firm can do and truly comply with the clear “risk based” requirement minimums set forth therein.</p> <p>Thus, the Agency should ignore this, at best, misguided request.</p>	<p>Please refer to Item A in the cover letter</p> <p>Properly, this draft guidance focuses its “risk management” discussions on the processes and operations and not “achieving quality.” This is the case because the risk-based CGMP regulations already have set the clear <b>minimum</b> requirements for “achieving quality” with respect to the “manufacture, processing, packing, or holding of a drug product” (including “packaging and labeling operations, testing, and quality control of drug products”).</p> <p>Apparently, this commenter lacks the requisite understanding of the clear CGMP quality minimums and, based on this, may need to revise its CGMP training programs to address this apparent CGMP deficiency.</p>
161, III. B	<p>Quality by design definition should include formulation as well as process design</p> <p>This reviewer cannot and does not support this commenter’s statement here.</p> <p>Hopefully, the Agency will simply ignore this, at best, unfounded comment.</p> <p>This reviewer again recommends changing the draft to read, “<i>Quality by design</i> means designing and developing manufacturing processes during the product development stage to consistently ensure <i>each unit produced meets all of its predefined quality criteria</i> at the end of the manufacturing process.”<sup>5</sup></p>	<p>The commenter provides no rationale for its remarks.</p> <p>Inexplicably, this commenter’s statement fails to recognize that the design of the formulation is an integral part of the design of the process.</p> <p>Again, the proper quality system’s goal for a pharmaceutical manufacturer should be to ensure that every unit, <b>not just those evaluated,</b> in each batch will, <i>if tested,</i> meet all of their predetermined <b>scientifically sound</b> and <b>appropriate</b> quality criteria – the public <b>generally</b> “consumes” the <b>untested</b> units.</p>

<sup>5</sup> These concepts are being developed under the ICH-Q8 Pharmaceutical Development Expert Working Group.

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer's Remarks</b>	<b>Rationale &amp; Reviewer's Basis</b>
171	<p>Please include the concept of risk assessment for changes to existing processes</p> <p>This reviewer does not agree with the commenter's statement and notes that the rationale provided not only does not support the comment but also, inexplicably, discusses a related, but different topic, "risk management." Moreover, the draft text is factually correct and on point. Hopefully, the Agency will simply ignore this statement.</p>	<p>As written risk management is a 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.</p> <p>Again, apparently, the commenter does not understand the clear requirement minimums of the CGMP regulations or the risk-based nature thereof.</p>
175, III D	<p>CAPA needs to be presented in a clearer manner. Corrective actions are those applied to a current discrepancy (such as repacking, rework, etc.). Preventive actions are those designed to prevent recurrence.</p> <p>This reviewer finds no need to present CAPA in a clearer manner and would suggest that this commenter should study the precepts of CAPA as it's remarks clearly do not indicate that this commenter understands CAPA. This reviewer hopes that the Agency will simply ignore this misguided comment.</p>	<p>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.</p> <p>Factually, this commenter is wrong in its assertions – a truly preventive action is one that prevents an occurrence – for example, changing the timing belt on a blender at 90,000 hours of operation when the part has a rated life of 100,000 hours to PREVENT belt failure during use.</p> <p>Using the same example, changing the belt replacement time to 90,000 hours after the belt has broken after 97,000 hours of use is corrective action.</p> <p>Hopefully, this simple example will help the commenter to better understand: CAPA and what is a truly preventative action, because its current remarks indicate that it does not.</p>
181, III D	<p>Please add the phrase in italics: Remedial corrections "to determine actions necessary for impact to all potential implicated batches".</p> <p>Again this reviewer objects on the grounds that this commenter has failed to learn the precepts of CAPA. This comment should also be simply ignored.</p>	<p>The other two bullet points clearly describe how the CAPA is used in operations</p> <p>The draft's text is on point and correct in its presentation of the three (3) concepts of CAPA as they are presented in most quality-oriented quality systems.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer's Remarks</b>	<b>Rationale &amp; Reviewer's Basis</b>
185. III E	<p>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.</p> <p>This reviewer sees no need for presenting the example alluded to by this commenter. Moreover, it would be counterproductive to discuss "what kind of changes a manufacturer is empowered to make" in a quality systems guidance. Such discussions, if needed, should be incorporated in guidances that address changes in manufacturing, processing, packing or holding and not in this guidance.</p> <p>For both reasons, this reviewer strongly suggests that these comments should simply be ignored as, at best, they are misplaced.</p>	<p>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.</p> <p>First of all, the commenter misstates the draft's topic, "change control," by referring to it as "change management."</p> <p>Second, the commenter misstates the proper purpose of "change management" which is, <i>under CGMP</i>, to manage all changes in manner that ensures that the process meets or exceeds its compliance minimums with respect to all applicable CGMP requirements and produces product such that each batch or lot (and not just the samples tested) meets or exceeds all of its predetermined scientifically sound and appropriate population-based specification.</p> <p>IF: a true build-quality-in approach has been adopted, THEN: there should be no need for any program "to allow for implementation of changes to facilitate continuous improvement" because a truly CGMP-compliant process should have little or no need for continuous improvement!</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
185	<p>This section should be clarified to state that in modern quality systems these are 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 CGMP requirements.</p> <p>This reviewer suggests that, at best, the tenor and remarks contained in these comments are at odds with certain of the clear CGMP requirements and would suggest that this commenter does not have the requisite training, experience and/or combination thereof as required by:  “§ 211.25 Personnel qualifications.  (a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee’s functions. <b>Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP</b> requirements applicable to them. ...”  At best, the commenter’s remarks should simply be ignored.</p>	<p>Oddly, the commenter provides no rationale for its remarks here.</p> <p>The commenter’s remarks are at odds with:  “§ 211.160 General requirements.  (a) The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, <b>including any change</b> in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, <b>shall be</b> drafted by the appropriate organizational unit and <b>reviewed and approved by the quality control unit.</b> ...,” the CGMP requirement that such decisions must be made by the firm’s mandated “quality control unit” (21 C.F.R. Sec. 211.22), and not by some “management team” as the commenter purposes.</p>
185, III E	<p>Please change the term “Change Control” to “Change Management”</p> <p>This reviewer has no problem with the commenter’s remarks and could support the use of the more-general term, “Change Management,” over “Change Control” provided the text remained fully compliant with all applicable CGMP <i>minimums</i>.</p> <p>However, as this reviewer pointed out in the comments he submitted to this docket, in reality all of the actions fall within the purview of the “Maintenance Qualification” (MQ) phase of the ongoing validation journey for each production process that begins in “Design/development Qualification” (DQ) and progresses to the MQ phase after the validity of fully function process has been established by a successful initial full-scale in-depth study of the initial production of product by such systems – an “Evaluation Qualification” (EQ) study or, more commonly, a “Performance Qualification “(PQ) study.</p> <p>Hopefully, those reviewing this commenter’s remarks and those of this reviewer will revisit this portion of the draft and generalize it into guidance that considers this section from the more global view of “Maintenance Qualification” (MQ) as they should.</p>	<p>Please refer to Item B in the cover letter</p> <p>If the commenter’s goal is, <i>as it should be</i>, to bring the terminology up to modern standards, then, a “life-long journey-based” approach that establishes that the process is valid should be adopted and changes should be addressed as integral parts of the maintenance of the qualification of the production processes and the batches of units produced by such production processes so that the process is provably valid at all times.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
196	<p>Please add “ability to measure the effect of a change” to the basis by which a manufacturer is empowered to make changes</p> <p>This reviewer does not support this change. A better approach, <i>and one that addresses the commenter’s concerns in a CGMP-compliant manner</i>, would be to change the draft text to read: “This means a manufacturer is empowered to make changes that reduce the variability in the critical characteristics of the incoming and in-process materials used in manufacturing and otherwise optimize the process to produce a more uniform or, <i>otherwise higher quality</i>, product through the ongoing CGMP-compliant use of statistical control techniques that permit the manufacturer to separate the effect of critical characteristic variation from random outcome fluctuation.”</p>	<p>An important aspect of change management is the ability to assure the change is not detrimental to overall quality. Without the ability to measure the effect of a change, a manufacturer can not determine the impact.</p> <p>The current regulatory environment with its “AR,” “CBE-0,” “CBE-30,” “supplement required,” and “compatibility protocol” options already provide the flexibility needed for changes. However, in practice, often the changes made not only do not improve product quality but also have the effect of actually reducing one or more of the critical quality characteristics of the product. This guidance should make it clear that a quality system’s approach does not permit any change that reduces any aspect of quality of the product. In the second instance, this guidance needs to make it crystal clear that statistical quality control (SQC) and statistics-based tracking and trending techniques should be used, <i>wherever possible</i>, in any quality system that is applied to pharmaceutical products because these are integral parts of today’s recognized good manufacturing practices and are therefore part of today’s CGMP as the term, “current good manufacturing practice, is used in 21 U.S.C. Section 351(a)(2)(B). Ideally, the goal of today’s CGMP-compliant systems should be to consistently produce product batches or lots that meet or exceed the quality standards associated with “Six Sigma” (a statistical standard that establishes a one-sided (above or below the true process mean, <math>\mu</math>, that has been established [<i>proven over an extended production period, or an appropriate number of batches</i>] for the process) expectation of finding all unit within 4.5 sigma of the true process mean, with the other side of the distribution of units (whichever side that is) for the process consistently falling within the 3-sigma limits implicitly established in 21 C.F.R. 211.165(d), “Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to assure that batches of drug products meet ... appropriate statistical quality control criteria as a condition for their approval and release,” by the use of the “shall” phrase, “... appropriate statistical quality control criteria ...”</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
207, III F	<p>Please add the phrase in italics: QC usually consists of testing of selected in-process materials, “raw materials” or “components” and finished products...</p> <p>The commenter remarks are clearly at odds with the clear CGMP requirements set forth in 21 CFR Part 211 and, as such, should be ignored.</p> <p>This reviewer finds that the commenter fails, as most do, to understand the difference between the “QC” function of review and approval and those personnel who report to QC (samplers and labs) who have the responsibility to properly sample and evaluate batch- or lot- representative samples at appropriate points in the incoming, in-process and final stage of production of the products produced.</p> <p>Based on the preceding reality, this reviewer would again recommend that the bullet be revised to read:</p> <p>“● QC usually consists of assessing the suitability of incoming components, containers, closures and labeling, critical in-process materials and the finished products to evaluate the performance of the manufacturing process to ensure adherence to proper specifications and limits, approve or reject materials “during the production process, e.g., at commencement or completion of significant phases or after storage for long periods,” and determine the acceptability of each batch for release.”</p> <p>Hopefully, the Agency will carefully assess this reviewer’s remarks and take them to heart when it proceeds to finalize this guidance.</p>	<p>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.</p> <p>This commenter suggests these changes to address the reality that while quality control is supposed to have “Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products” (21 C.F.R. Section 211.22(b)), quality control <b>must</b> “have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, ... The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company” (21 CFR Sec.211.22(a)).”</p> <p>This distinction is increasingly important as more and more manufacturers <i>outsource</i> their sample evaluation programs to contract laboratories leading to the reality that increasingly such manufacturer’s on-site laboratories that directly report to the QC function do less and less sample evaluation. <b>[Note:</b> In some cases, some firms may be also effectively improperly outsourcing a part of the required incoming material sampling program when they allow their supplier to provide pre-shipment samples of incoming materials that these firms then send out to a contract laboratory for evaluation and, <i>when the results are reported to meet their manufacturing specifications</i>, releasing those incoming lots for use without having sampled them as required in 21 C.F.R. Sec. 84.]</p>

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217, III F	<p>“The cGMP (sic) 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.</p> <p>Because the commenter’s remarks are at odds with a clear binding regulation, the Agency cannot legally incorporate the changes suggested into this guidance.</p> <p>Moreover, <i>by suggesting such changes</i>, the persons who wrote this comment are either: <b>a)</b> ignorant of regulations that they are supposed to know <b>or b)</b>, <i>if they are aware of said regulations</i>, knowingly advocating a subversion of the regulatory process, an activity which could be an actionable.</p> <p><i>With respect to the text under discussion</i>, this reviewer would suggest the following alternative wording:</p> <p>“The CGMP regulations specifically assign the quality unit the authority to create, monitor, approve, and implement the quality system and any change thereto.”</p> <p>Hopefully, the Agency will carefully consider this reviewer’s comments and act appropriately.</p>	<p>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.</p> <p>First, this reviewer disagrees with this commenter’s naive characterization that “Quality systems are for the most part cross functional systems” because this simplistic generalization is, <i>for the most part</i>, clearly not true.</p> <p>Second, the CGMP regulations clearly establish the responsibilities and, directly and indirectly, the authorities of the “quality unit” which settles this issue, even though this reviewer often finds that many companies seem to knowingly ignore this law when there is a product problem.</p> <p>The changes suggested by this reviewer are intended to explicitly recognize that the approval and modification of the quality system also fall within the purview of the authority of the quality unit – and NOT some cross-functional “team” in which the quality unit is “outvoted” by the members of the other corporate units on such cross-functional “teams” – most often the participating members from the operations, manufacturing, and senior management units.</p> <p>Having been repeatedly subjected to such systems, this reviewer knows that such are pervasive in the pharmaceutical industry and the Agency is aware, and appears to have turned a proverbial “blind eye” to such activities and the SOPs that permit such in the firms that engage in such practices.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
222, IIIF	<p>Validation and Quality Planning should be added to this statement.</p> <p>This reviewer does not agree with the commenter’s suggestion here, because these are activities that fall under the responsibilities explicitly set forth in the pertinent sections of the CGMP regulations.</p> <p>However, this reviewer does recommend changing the text in Lines 222-232 as follows:</p> <p>“Other CGMP assigned responsibilities of the quality unit are consistent with a modern quality system approaches (see § 211.22):</p> <ul style="list-style-type: none"> <li>• Ensuring the controls are scientifically sound and appropriate as well as ensuring that the samples sampled and the samples evaluated are representative of the population (batch or lot) from which they are taken.</li> <li>• Ensuring that controls are implemented and completed satisfactorily during manufacturing operations</li> <li>• Ensuring that developed procedures and specifications are appropriate and followed, including those used by a firm under contract to the manufacturer</li> <li>• Approving or rejecting incoming and in-process materials, and drug products — although such activities do not substitute for, or preclude, the daily responsibility of other unit’s personnel to build quality into the product</li> <li>• Reviewing production records and overseeing the investigation of any unexplained discrepancies”</li> </ul> <p>Hopefully, the Agency will reject the attempt to treat “Validation” and “Quality Planning” as other than the “control” activities that they so obviously are.</p> <p>The commenter’s remarks are apparently an indication of this commenter’s aversion to the “controls” view of the CGMP regulations for finished pharmaceuticals.</p>	<p>These are important aspects of a quality system</p> <p>Both “Validation” and “Quality Planning” are activities that fall within the umbrella of control of the process and are, therefore, do not belong at the “control level” outlined in this section of the guidance.</p> <p>The first inserted bullet, “Ensuring the controls are <i>scientifically sound</i> and <i>appropriate</i> as well as ensuring that the <i>samples</i> sampled and the <i>samples</i> evaluated are <i>representative</i> of the <i>population</i> (batch or lot) from which they are taken,” was added to ensure that the reader recognize that the “scientifically sound” and “appropriate” are the foundation of any modern quality system for a CGMP-compliant pharmaceutical process (21 CFR Sec. 211.160). In addition, this bullet sets forth the need for <b>all samples</b> to be <i>population representative</i> because the goal of a CGMP-compliant quality system must be to ensure that the <b>untested samples</b> probably meet all of their specifications. A corollary to the preceding is that, <u>unless</u> a <i>scientifically sound</i> and <i>appropriate representative sample</i> is evaluated, the results from any sample evaluation <b>cannot</b> be used to do what is required, <i>namely</i>, predict <i>with a high degree of confidence</i> that the <i>unevaluated units</i> meet all of their specifications.</p> <p>The suggested change in the bullet that begins “Approving or rejecting ...” should be made because, <i>if you are going to build quality in</i>, you <b>must</b> start doing so during development. Moreover, a manufacturer <b>cannot</b> build in quality if that manufacturer does <b>not</b> address and appropriately control the quality of all of the incoming materials used in the process!</p> <p>The suggested change in the last bullet recognizes that the quality unit should appropriately <b>oversee</b> the conduct of any production discrepancy investigations because the production unit that generated the discrepancy is usually better equipped to conduct the investigation than the quality unit <i>per se</i>. <b>[Note:</b> In this context, the laboratories reporting to the quality unit are production units – whether contract or in-house, <i>labs</i>, or <i>other operational unit or computerized system that properly evaluates an appropriately representative set of samples, produce sample evaluation results for the quality unit’s review and decision-making responsibilities.</i>]</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
229	<p>Add “raw material or “component’s following the word “rejecting”</p> <p>Though this reviewer does not disagree with the needs to address components, other items that need to be addressed include containers, closures and labeling.</p> <p>Thus, the global term that should be added is “incoming materials” (<b>see</b> Row “222, IIIF” for this reviewer’s suggested text).</p>	<p>Release of raw materials and components is an important aspect of the QC function. Addition of these items completes the listing of items used throughout the process.</p> <p>(<b>See</b> this reviewer’s basis statements in Row “222, IIIF.”)</p>
230, III F	<p>Add the word “other” prior to the word “manufacturing”</p> <p>This reviewer disagrees with this commenter because all units, including the top management and personnel units, for example, are part of the overall quality system.</p> <p>Thus, this reviewer again suggests that the Agency revise the draft here in the manner suggested in his remarks in Row “222, IIIF.”</p>	<p>To clarify that the quality unit although separate is part of the overall manufacturing operation.</p> <p>(<b>See</b> this reviewer’s basis statements in “222, IIIF.”)</p>
232	<p>Change “reviewing production records and investigating any unexplained discrepancies” to “actively participating in the investigation of any unexplained discrepancy”</p> <p>This reviewer does not disagree with the suggested change.</p> <p><i>Given the clear CGMP requirements</i>, he suggests that the quality unit’s true function is one of oversight as he stated in Row “222. IIIF.”</p>	<p>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.</p> <p>(<b>See</b> this reviewer’s basis statements in Row “222, IIIF.”)</p>
235, IVA2	<p>Please add in that the Quality Unit Manager should have the authority to detect problems and affect solutions.</p> <p>This reviewer sees no basis for this commenter’s title-specific statement.</p> <p>Since this commenter provides no rationale for its comment here, this reviewer suggests that it be ignored.</p> <p>However, this text does need to be revised to read:</p> <p><i>“Under a robust quality system, the product and process development units, manufacturing units, and the quality unit can remain independent, but still be included in the total concept of producing quality products. Although staffing levels should be reflective of the size of the operation, the number of individuals assigned to the quality control unit must be sufficient to meet the requirements of 21 CFR § 211.22 and other applicable regulations. The quality unit is accountable for reviewing, approving, and overseeing the implementation of all the controls, and for ensuring that product quality standards have been met.”</i></p>	<p>The commenter provides no rationale for its remarks.</p> <p>The need to explicitly include the “<i>product and process development units</i>” in the list of units outlined in a “robust quality system” stems from the reality that building quality into a product must begin with those who interactively develop both the product and the process for its manufacture.</p> <p>In addition, the general approval or rejection authorities of the “quality unit” should also be explicitly included here</p>

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272, III G	<p>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.</p> <p>While this reviewer sees no need to list the “six ... systems,” outlined in the figure (only one is a “quality” system), he does not object to doing so. However, because this guidance is intended to address the links between quality systems and the CGMP regulations for drugs and finished pharmaceuticals, this reviewer does object to linking the “Six System Inspection Approach” to the <b>four-part “Quality System Model”</b> (Management Responsibilities, Resources, Manufacturing Operations and Evaluation Activities), outlined in this guidance.</p> <p>Based on this reviewer’s remarks and supporting basis statement and the commenter’s rationale, the Agency should simply ignore this commenter’s suggested changes here.</p>	<p>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.</p> <p>Apparently, the commenter did NOT count the number of subsystems in the figure and has obviously confused the figure’s one quality system and five operational systems with “quality systems.”</p> <p>Further, the commenter’s rationale does not provide any logical support for the comments made about linking an FDA inspection system model (in which the operational areas fall under the quality system) presented in the figure under discussion with the “Quality Systems Model” that follows this figure.</p>
282, IV	<p>Please add in phrase in italics: This section describes a robust quality system that if “designed”, implemented and “operated properly” could provide.....</p> <p>This reviewer does not support the changes suggested by the commenter because:</p> <ol style="list-style-type: none"> <li>1. The commenter’s have misread or deliberately changed the original text, “robust quality systems model,” in a manner that is at odds with the topic under discussion (a robust quality systems model”)</li> <li>2. Since the topic is a particular defined “model,” there is no need to “design” this already clearly designed model.</li> <li>3. The commenter further confuses the “model” (which cannot be operated) being discussed with the operations the “model” addresses.</li> </ol> <p>However, this reviewer does suggest changing the text to read:  “<i>This section describes a robust quality systems model, which, if properly implemented, can provide the controls needed to consistently produce a product of more than acceptable quality.</i>”</p>	<p>It is not enough to implement</p> <p>This reviewer can only agree that it is not enough to just implement a “robust quality systems model.”</p> <p>A firm must <b>properly</b> implement that model if that firm is to realize its expectations. Thus proper implementation is a critical component if the manufacturer is to meet expected outcomes. Many of the recent major product failures can be traced to improperly implemented quality systems.</p> <p>In addition, the goal must be processes that consistently produce <b>more than</b> acceptable quality to ensure that, <i>when the worst-case variabilities occur</i>, the product produced should still be acceptable. <i>For processes that vary</i>, those who set their target at merely producing acceptable product are tolerating the fact that such processes do produce some fraction of unacceptable product units.</p> <p>Ideally, <i>in a robust quality system</i>, the target for product quality should be set sufficiently higher than the least acceptable quality by an amount sufficient to ensure that, with a high level of confidence (95 % or higher), the probability of producing a product with unacceptable quality is less than one in some multiple (usually, 3 or higher) of the quantity of product produced in any given period (typically, a year).</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer's Remarks</b>	<b>Rationale &amp; Reviewer's Basis</b>
306, IV A	<p>Please add in phrase in italics: in the design, implementation, “monitoring and continuous improvement” of the quality system.</p> <p>The commenter's misplaced statement should be ignored.</p>	<p>Continuous improvement is an important aspect of quality systems.</p> <p>While continuous improvement may be “an important aspect of quality systems,” it is NOT an aspect of the “quality system model,” the topic under discussion here.</p>
311, IV A	<p>Please add in phrase in italics: in the design, implementation, “monitoring and continuous improvement” of the quality system.</p> <p>Again, this commenter's misplaced statement should be ignored.</p>	<p>Continuous improvement is an important aspect of quality systems.</p> <p>Again, while continuous improvement may be “an important aspect of quality systems,” it is NOT an aspect of the “quality system model,” the topic under discussion here.</p>
317, IV A 1	<p>“Align quality plans with the manufacturers...” please delete the word “system”</p> <p>This commenter continues to confuse the overall “quality system” with its implementation and component parts.</p> <p>Moreover, this commenter seems to be deliberately trying to change the subject of the text from one of “plans” to one of “planning.”</p> <p>Since the guidance is correctly addressing the overall “quality system” plan here, this commenter's change should be ignored.</p>	<p>Quality Planning is a process that is a part of a quality system. A section on quality planning would be beneficial.</p> <p>Apparently, having become confused about the topic under discussion, this commenter further attempts to confuses “quality system plans” with “quality planning,” a subject that is not being addressed and one that is not pertinent to the topic under discussion, “<b>IV. The Quality System Model, A. Management Responsibilities, 1. Provide Leadership.</b>”</p>
328 IV A 1	<p>It should be noted that a quality system need not be global to be effective. A single site can be successful.</p> <p>While the commenter's statements are true and different quality systems models may be implemented in different sites, this reviewer understands that a firm's overall quality system is most effective when it is the same in all of the firm's facilities.</p> <p>Should the Agency elect to add this commenter's statement to the guidance, this reviewer suggests that this reviewer's remarks should also be added.</p>	<p>The commenter provides no rationale for its remarks.</p> <p>As long as the processes and products fully comply with the CGMP <b>minimums</b> set forth in 21 C.F.R. Parts 210 and 211, the FDA is required to accept the quality system. Therefore, different “quality systems” in different facilities is permitted.</p> <p>However, given the advantages offered by the implementation of a single robust CGMP-compliant quality system globally, this reviewer would recommend that this approach be used whenever it is possible to do so.</p>
331	<p>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.</p> <p>This reviewer does not support the inclusion suggested by this commenter here.</p>	<p>Consistent with QSR requirements for Management Responsibility (§ 820.20)</p> <p>The commenter continues to confuse the model and the discussion appertaining thereto with the implemented quality system.</p> <p>The commenter attempts to separate management into groups (“management and senior management”) when no such separation is appropriate since the discussion in the guidance here pertains to the management function and not how it is implemented.</p>

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346, IV A 2	<p>Please focus on individual system owners here rather than the Quality System.</p> <p>Given the topic, “IV. The Quality System Model, A. Management Responsibilities, 2. Structure the Organization” and the reality that <i>management by committee</i> is recognized as a less than desirable approach to managing any system, this reviewer cannot support the commenter’s suggestion</p>	<p>The focus would be better placed on individual systems owners 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.)</p> <p>Since the topic being discussed is the “Quality System Model,” this commenter’s remarks are, at best, misplaced. Further, this reviewer would suggest that the commenter accept the factual reality that the “Quality System Model” being discussed is composed of a set of four (4) subsystems and frame their comments and rationales within that framework.</p>
358, IV A. 3	<p>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.</p> <p>This reviewer cannot support the commenter’s suggestions here. However, this reviewer does suggest changing the text in Lines 353-365 to read:  “Implementing a robust quality system can help ensure compliance with regulations related to safety, identity, strength, quality, and purity as long as the quality system meets or exceeds the requirement <i>minimums</i> of CGMP regulations as well as meets the needs of the manufacturer. Under the quality systems model, the Agency recommends that senior managers ensure that the quality system they design and implement provides clear organizational guidance and facilitates systematic evaluation of issues. For example, according to the model, when documenting a quality system, the following should be included.</p> <ul style="list-style-type: none"> <li>• ...</li> <li>• ...</li> <li>•</li> <li>• The procedures needed to establish and maintain the quality system</li> <li>• The proofs that establish that the quality system meets the requirement minimums of the applicable CGMP regulations.”</li> </ul>	<p>The commenter provides no rationale for its remarks.</p> <p>The commenter’s statements not only deliberately ignore the topic under discussion but also clearly indicate that this commenter has failed to understand that the text addresses the clear “Quality Systems Model” that is the root subject (“IV. The Quality System Model”) being discussed. However, this reviewer does suggest revising the draft’s text because, to be CGMP compliant, a quality system must meet or exceed all of the applicable CGMP <i>minimums</i> (see 21 CFR Sec.210.1 and 21 CFR Sec. 211.1(a), “The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.”).</p> <p><i>Since the CGMP regulations at 21 CFR Sec 211.160(a) require the covered firm to establish their “specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, ...”, and inherent in “establishing” any control is the element of proof, the manufacturer must have proof that establishes the validity of said controls (including the quality system itself).</i></p> <p>For these reasons, and other similar reasons, outlined in this reviewer’s formal comments to this docket, this reviewer recommends making the text changes and additions suggested.</p>

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367, IV A. 3	<p>Change the word from “directives” to “management”</p> <p>This reviewer, understanding that “directives” means “written orders” including items such as “policies, plans, specifications, and procedures (SOPs and work instructions), opposes the change suggested by this commenter.</p>	<p>It is unclear as to which directives FDA is referring to. Management makes better sense. If this is incorrect, please clarify.</p> <p>Apparently this commenter failed to read the rest of this paragraph in which it becomes clear that the “directives” in question are, among other things, those “controls for specifications, plans, and procedures that direct operational and quality system activities.”</p>
391, IVA4	<p>Please clarify that objectives should be quality objectives for the site and should be placed within the quality plan.</p> <p>Though from the first sentence in this paragraph, it is clear that the only objectives being discussed here are quality objectives, this reviewer would support changing the text in lines 388-393 to read: “Managers operating within a quality system are expected to define the quality objectives needed to implement the quality policy. 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 planning process. These quality objectives are typically aligned with the manufacturer’s strategic plans. A quality system seeks to ensure that managers support these quality objectives with necessary resources and have measurable goals that are monitored regularly.”</p> <p>However, given the topic, this reviewer does not support the commenter’s request to state where these quality objectives should be placed</p>	<p>It is preferable not to review personal objectives as some elements could be outside of the agency’s inspectional authority.</p> <p>Given this commenter’s failure to consider each statement in this paragraph within its context in that paragraph, this reviewer sees that, to prevent others from taking this statement out of context, the text should be revised even though such is not, <i>per se</i>, required</p> <p>This reviewer sees no need for explicitly stating that the objectives being discussed “should be placed within the quality plan” because the requisite “formal quality planning process” obviously generates the quality plan and, <i>within that plan</i>, appropriately places each quality objective. This commenter seems to need to carefully reread this paragraph in its context – the guidance’s “formal quality planning process” obviously expects that process to generate the firm’s quality plan.</p>
395, IV A 4	<p>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.</p> <p>This reviewer sees no need to add the commenter’s suggested text here. If any addition is needed, this reviewer would suggest adding:</p> <p>“For preexisting or contract facilities, quality planning should be aligned, <i>to the extent possible</i>, with the existing facility realities. In all other cases, the facility planning process is but one subsidiary facet of a firm’s overall quality planning activities.”</p>	<p>This achieves the holistic approach to quality discussed in the introductory sections.</p> <p>Since a holistic approach to quality starts quality at the design/development phase of the life of a drug product and its production process, holistic quality planning obviously precedes “the overall plant planning process.” For existing facilities, quality planning should be aligned with “the overall plant planning process.”</p> <p>Thus, the correct statement is one that clearly states that the overall plant-planning process for a new facility is one facet of quality planning.</p>

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395, IV A .4	<p>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.</p> <p>This reviewer does not understand what quality planning has to do the internal audit process. Moreover, given the clear “establish” (prove) mandates in the CGMP regulations, it is, or should be, clear that all facets of the quality planning are as subject to Agency inspection as the current compliance planning systems.</p>	<p>For a quality planning system to be effective, parts will be outside of inspection jurisdiction.</p> <p>The is reviewer finds no validity in the commenter’s assertion that parts of any quality planning system are somehow outside of the FDA’s authority to inspect for:</p> <p><b>a.</b> Compliance to the systems in place and <b>b.</b> Proof that the systems in place fully comply with not only all CGMP requirements but also any other self-imposed requirements adopted by the regulated firm.</p>
395	<p>Change “identify resources” to “allocate resources”</p> <p>This reviewer cannot support this commenter’s obviously misplaced suggestion.</p>	<p>In order to have an effective quality system, resources must be allocated not just identified.</p> <p>Since the sentence in question states, “Under a quality system, managers would be expected to use quality planning to identify resources and define methods to achieve the quality objectives,” the sentence properly states the goals of the <b>planning</b> process. Unless, in planning, the resources required are identified, <i>when the plan is later implemented</i>, the required resources cannot be assured of being available for allocation.</p>
404, IV A 5	<p>Please add the phrase in italics: ..conduct reviews if the “performance of the quality system..”</p> <p>This commenter does not support the change suggested because it insupportably limits the scope of the suggested review of the whole quality system.</p> <p>Further, he finds that the comment here is not only unwarranted but also anti-quality.</p>	<p>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.</p> <p>First of all, the suggested management review of the “whole quality system” is in no way restricted to either the commenter’s stated “review of the design” or the requested limitation (“performance of the quality system”) but is intended to review, as the text states, all facets of the “whole quality system.”</p>
405	<p>Please add the phrase in italics: typically includes both an assessment of the product “and process” as well as the customer needs.</p> <p>This reviewer has no problem other than to suggest that, <i>for completeness and grammatical correctness</i>, the inserted text should be revised to read, “the incoming and in-process materials used to produce the finished product, the drug product produced, and the process.”</p> <p>In addition, the word “both” after the word “includes” should be stricken from this sentence.</p>	<p>This acknowledges that quality systems should address the process not just the product meeting specifications</p> <p>Most who are familiar with quality systems understand that any quality-system review assessment of a product (or service) implicitly includes a review of the incoming and in-process materials and process used to produce that product (or service).</p> <p>However, this reviewer has no problem including the wording suggested.</p>
415, IVA5	<p>It is unclear how this will be measured. This bullet point should be deleted unless there can be guidance as to clear measurement techniques.</p> <p>This reviewer does not agree with the commenter. Based on the clear examples provided, it is obvious that this bullet should be retained because there is no valid “measurement” issue.</p>	<p>The commenter provides no rationale for its remarks.</p> <p>Since the bullet states, “Any changes in business practices or environment that may affect the quality system (such as the volume or type of operations),” it is obvious that it is subject to judgment and properly exemplified.</p>

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417	<p>Please add in a review of quality system indicators such as complaints, deviations, changes, and Annual Product Reviews</p> <p>This reviewer finds that this comment clearly indicates that the commenter failed to read and understand the previous bullets. The reviewers' basis analysis clearly establishes that the requested changes should be rejected. Hopefully, after carefully reading this reviewer's basis statements, the commenter will withdraw this comment.</p>	<p>A comprehensive review of these indicators assure continuous improvement and communication of the systemic issues to senior management.</p> <p>Apparently this commenter overlooked (<b>bolding</b> added): Line 411, "Customer feedback, including <b>complaints</b>"; Line 410. "The <b>results of</b> audits and <b>other assessments</b>," which would seem to encompass both "deviations" and "changes" as well as Line 413, "The status of actions to prevent a potential problem or a recurrence" and Line 414, "Any follow-up actions from previous management reviews" which <b>obviously</b> include "changes" and, in some cases, "deviations"; and Line 412, "The analysis of data trending results" which obviously includes "Annual Product Reviews." Moreover, the suggested "Annual Product Reviews" item is obviously at odds with the commenter's stated rationale for "continuous improvement" because, by their very "Annual" nature, such reviews are definitely less than continuous.</p>
419	<p>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.</p> <p>This reviewer sees no need to so limit the agenda of such meetings. If any change is needed, this reviewer would suggest the following: "Outside of scheduled reviews, the quality system, including but not limited to key quality indicators, changes and proposed changes, deviations and other pertinent issues, is typically included as a standing agenda item in general management meetings"</p>	<p>A review of specific items as part of the quality system is imperative for communication and specific areas of improvement</p> <p>Though the commenter's statement may be accurately presenting the imperatives within its own organization, all aspects of a firm's quality systems should be open to discussion in any "general management meeting." As a compromise, this reviewer proposes including the item mentioned (in its correct form, "key quality indicators" as opposed to the commenter's nebulous "the 'key indicators of' the quality system."</p>
426, IVA5	<p>It will need to be clarified that these recorded results of the management review are considered internal audit documentation</p> <p>This reviewer does not agree with either the comment or commenter's off-the-subject "rationale." This unsupported comment should therefore simply be rejected.</p>	<p>For a quality planning system to be effective, parts will be outside of inspectional jurisdiction.</p> <p>Since management review so obviously falls outside of the Agency's general policy "except for cause" exemption for internal audit documents, this reviewer is surprised that this commenter even attempted to proverbially "grasp at this straw." In addition, the rationale provided does not even directly address management reviews.</p>

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447, IV B1	<p>Suggest deletion of the word “sufficient”</p> <p>This reviewer does not agree with the commenter’s suggestion and recommends that the word “sufficient” should be retained here.</p>	<p>It is unclear how “sufficient allocation” of resources will be measured.</p> <p>Since the rest of this paragraph and its bulleted items define the areas where resources are needed, it should be clear that the sufficiency of such is measured by the system’s success in operating in control and producing quality product. Thus, the commenter’s stated concern is, at best, a proverbial “straw dog.”</p>
449, IV B1	<p>Please include a role for all employees instead of a defined role only specified for senior management.</p> <p>Given the topic being discussed, “<b>IV. The Quality System Model, B. Resources, 1. General Arrangements,</b>” the general responsibility for providing resources clearly rests with senior management.</p> <p>Based on that reality, this reviewer cannot support this commenter’s misplaced request.</p>	<p>Under a quality system employees should also be expected to play an active role in monitoring and controlling the systems/processes they work with.</p> <p>While the preceding is true, it does not apply to the general topic being presented in this section of the guidance.</p> <p>Since providing the requisite resources is clearly a major responsibility for senior management, the text should not be changed here as the commenter suggests.</p>
455, IV B	<p>Warehousing should be included as an additional bullet point.</p> <p>While agreeing that providing the resources for warehousing, and other operations is important, this reviewer suggests addressing such by changing the draft’s Lines 452-456 to read:</p> <ul style="list-style-type: none"> <li>• To supply and maintain the appropriate facilities and equipment to consistently manufacture a quality product in compliance with CGMP (see §§ 211 Subparts C &amp; D)</li> <li>• To acquire and receive materials, including labeling, that meet or exceed their applicable established CGMP minimums and are suitable for their intended purpose (see §§ 211 Subpart E and 211.122)</li> <li>• For processing the materials <i>in a CGMP-compliant manner</i> to produce the finished drug product (see § 211 Subpart F)</li> <li>• For packaging and labeling of the finished drug product into finished packaged drug product (see §§ 211 Subpart G and 211.160(b)(1))</li> <li>• For the CGMP-compliant laboratory analysis of incoming (see §§ 211.84(d), ...87, ...94(d), and ...122(a)) and in-process materials (see §§ 211.110 and ...160(b)(2)) and the finished drug product (see §§ 211.160(b)(3), ...165, ...166 and ...167), including the collection, storage, and examination of representative incoming material (see §§ 211.160(b)(1)), in-process (see §§ 211.160(b)(2)), stability (see §§ 211.160(b)(3) and ...166), and reserve samples (see § 211.170)</li> <li>• For the CGMP-compliant acceptance or rejection of each batch or lot of drug product for release for distribution (see § 211.165) using representative sample evaluations (see § 211.160(b)(3)) and statistical quality control (see § 211.165(d))”</li> </ul>	<p>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.</p> <p>By adding specific references to §§ 211 Subparts C &amp; D in the first bullet, all the issues raised by the commenters along with other similar issues are addressed without adding a separate bullet point for each.</p> <p>In addition, the changes made have been introduced to better align the text with the clear CGMP requirement minimums and provide suitable references for each item in the bulleted items.</p> <p>Finally, the last bullet was added because this is one quality system’s “CGMP requirement <i>minimum</i>” area that many manufacturers, processors, and packers seem to simply ignore, and the Agency has not only repeatedly refused to take the requisite corrective actions to bring these organizations into compliance but also approved submissions in which these firms seemingly failed to provide for the CGMP-compliant evaluations of representative finished pharmaceutical units sufficient to meet the “statistical quality control criteria” requirement set forth in 21 C.F.R. Sec. 211.165(d).</p>

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456, IV B	<p>There should be a bullet added for resources to operate the quality system.</p> <p>This reviewer agrees and suggests adding a final bullet that reads,</p> <ul style="list-style-type: none"> <li>• To supply the resources needed to operate the firm’s quality system.”</li> </ul>	<p>This is consistent with the concept of resource allocation.</p> <p>This reviewer has no problem explicitly including the resources for operating the organization’s quality system.</p>
462, IV B. 2	<p>Change “cross-cutting” to “cross-functional”</p> <p>This reviewer agrees with the commenter’s suggestion here.</p>	<p>More conventional and cleaner terminology</p> <p>The term “cross-functional” is more appropriate than “cross-cutting” because it carries with it no connotation of aggression.</p>
474, IV B 2	<p>Please separate the training element of a quality system as its own section.</p> <p>This reviewer recommends the commenter’s suggestion should be ignored because it is neither supported by the CGMP-approach to training nor consistent with the “<b>Quality System Model</b>” upon which this guidance is based.</p>	<p>Training is an integral part of every quality and manufacturing system.</p> <p>This reviewer agrees with the commenter’s statement but notes that “integral part” does not mean that it is or should be separated out. Moreover, the applicable CGMP regulations subpart:</p> <p>“21 C.F.R. Subpart B—Organization and Personnel  § 211.22 Responsibilities of quality control unit.  § 211.25 Personnel qualifications.  § 211.28 Personnel responsibilities.  § 211.34 Consultants.”</p> <p>does not put training in a separate section. In addition, other management systems also do not make training a standalone section. Further the topic being discussed is “<b>IV. The Quality System Model, B. Resources, 2. Develop Personnel</b>” – a topic that does not lend itself to separating training from the other aspects of developing personnel.</p>
487	<p>Please add in the phrase in italics: Evaluation of effectiveness of training “to assure learning or knowledge transfer has occurred”</p> <p>This reviewer does not support this unnecessary and incomplete addition requested by the commenter in this entry.</p>	<p>The addition helps define the purpose of the evaluation</p> <p>Apparently, this commenter has deliberately chosen to ignore the stated purpose inherent in the draft’s text, “<b>Evaluation of effectiveness</b> of training” (bolding added for emphasis). <b>[Note:</b> If a firm is truly determining that training is effective, it is, of necessity, not only assuring that “learning and knowledge transfer has occurred’ but also that the persons trained truly understand what they have learned and can effectively apply and are applying that understanding in the discharge of their duties.] The purpose of the evaluation is, or should be, obvious – to determine the training’s <b>effectiveness</b> and no additional verbiage is needed.</p> <p>Since effectiveness encompasses all of the areas mentioned by the commenter and this reviewer, there is no need to be redundant here.</p>

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499, IV B 3	<p>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.</p> <p>This reviewer does not support the commenter's statement and recommends that the Agency ignore it.</p>	<p>The commenter provides no rationale for its remarks.</p> <p>Apparently, this commenter does not believe the FDA should state what assistance it can provide and would rather change what the FDA is able to do to address the same subject in other terms. Moreover, understanding the FDA's regulatory constraints and resource limitations, this reviewer sees no basis for the commenter to suggest revising the draft in this instance.</p>
515	<p>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</p> <p>Since this reviewer sees no point to the commenter's less than focused comments and their supposed rationales, these statements should simply be ignored.</p>	<p>Current 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.</p> <p>The guidance provided is not only clear here but also congruent with the clear requirement <i>minimums</i> of the CGMP regulations.</p>
523, IVB4	<p>It is unclear whether the agency will allow a contractor to be authorized to release final product</p> <p>This reviewer cannot agree with commenter's overly broad generalization here. Since no changes are suggested, this reviewer recommends that the commenter's statement simply be ignored.</p> <hr/> <p>Since most quality units lack the absolute and unfettered authority to enter into binding contracts for their firm, this reviewer does not see how the quality unit can, <i>without requiring the approval of any other business unit, including top management and the business units responsible for administering contracts</i>, so act and still comply with clear CGMP requirement minimum set forth in Sec. 22(a).</p> <p>Moreover, the Supreme Court has held that drug firms have the absolute non-dischargeable responsibility for the drugs they produce and then introduce into commerce.</p> <p>Given both of the preceding realities, this reviewer sees no CGMP-compliant way for a firms' quality unit to legally delegate or otherwise "outsource" their authority to release a drug into commerce to any contractor <u>unless</u> the contractor's quality unit is directly controlled by, directly reports to, and directly paid by, the manufacturer's quality unit (QU) or, in other words, directly a part of said QU.</p>	<p>If a contractor has good quality systems as determined by audit, history, etc., the contract giver should be able to delegate authority to release product.</p> <p>Given that the minimum standard for CGMP compliance set forth in 21 C.F.R. Section 211.22(a) clearly states (<b>bolding added for emphasis</b>),</p> <p><b>"There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company"</b></p> <p>it would seem that CGMP-regulated firms would not be in compliance if they "delegated" this responsibility to another firm.</p> <p>This reviewer cannot see how a quality unit can be responsible, <i>as it is required to be</i>, for "approving or rejecting drug products" <u>unless</u> it makes the approve/reject decision.</p>

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545, IV C 1	<p>Suggest adding technology transfer from R&amp;D to production as a quality system.</p> <p>This comment should simply be ignored.</p>	<p>The commenter provides no rationale for its remarks.</p> <p>This commenter provides no supporting rationale for the comment made. Moreover, the comment made is both:</p> <p><b>a.</b> Ambiguous and</p> <p><b>b.</b> Clearly at odds with the integrated, seamless, “cradle (design) to grave (production cessation),” quality systems’ approach espoused in the text supporting the model outlined in this guidance.</p>
558, IV C 1	<p>Expand from “validation activities” to “process control activities”</p> <p>This reviewer cannot support the change suggested by the commenter here.</p>	<p>Validation is too limiting a concept.</p> <p>This reviewer finds it is the commenter’s understanding of “Validation” that is too limited and not today’s FDA-accepted concept that “Validation” is a life-long journey for both the process and the product produced by that process. Moreover, “Validation” extends beyond “process control activities” to encompass the monitoring and acceptance or rejection of incoming and in-process materials and the final drug product.</p> <p>Thus, it is “process control activities,” <i>and not “Validation,”</i> that is the more limited concept in the view of both the FDA and those that truly understand that “Validation” is a life-long “is valid” journey that starts with the birth and early development of both the drug product and the process used to make the drug product, and continues, by stages usually labeled as some type of qualification, until either the drug product ceases to be made or, in the case of the process, the current process is retired in favor of a new process.</p>
559	<p>Change from “effects” to “interaction of”</p> <p>This reviewer objects to the commenter’s proposed change because it is at odds with the quality systems’ approach being discussed here. However, this reviewer does see that the current test should be slightly revised to read, “This documentation includes:</p> <p>...</p> <ul style="list-style-type: none"> <li>• Effects on related processes, functions, or personnel”</li> </ul>	<p>Interaction is a broader concept</p> <p>It is not the breadth of a concept but its appropriateness of the concept that should determine whether or not a proposed change should be considered. As revised by this reviewer, the text states: (<b>bolding</b> added for emphasis)</p> <p>“<b>This documentation includes:</b></p> <p>...</p> <ul style="list-style-type: none"> <li>• <b>Effects on related processes, functions, or personnel”</b></li> </ul> <p>From the context, it is clear that the current wording, “Effects on ...” is more appropriate than “interaction of ...” and that the only change needed is to change “process” to “processes.”</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
569, IV C 2	<p>It is unclear if this is applicable only to packaging and labeling or to all manufacturing operations. Labeling will be discussed as a system, including its general inputs and outputs, and the critical interfaces to other systems.</p> <p>This reviewer rejects the commenter’s initial statement because it ignores the clear title and the explicit text and recommends that these comments be ignored.</p> <p>However, this reviewer does recommend moving the first paragraph in this section so that it becomes section “4.” and the existing sections “3.” and “4.” become sections “2.” and “3.” respectively. In addition, this reviewer recommends moving the second paragraph of the current section “2.”:</p> <p>“In modern quality systems environments, when new or reengineered processes are developed, it is expected that they will be designed in a controlled manner. A design plan would include authorities and responsibilities; design and development stages; and appropriate review, verification, and validation. If different groups are involved in design and development, the model recommends that responsibilities of the different groups be documented to avoid omission of key duties and ensure that the groups communicate effectively. Plans should be updated when needed during the design process. Prior to implementation of processes (or shipment of a product), a robust quality system will ensure that the process and product will perform as intended. Change controls should be maintained throughout the design process.”</p> <p>and placing it in its own section, “7. <i>Improve Process</i>” (a section that is presented with a slightly different title and text in the reviewer’s formal comments to the docket), because this paragraph addresses general “process improvement” issues that apply globally.</p>	<p>This will then serve as an example for other systems not covered in this guidance.</p> <p>Since the section is titled, “Monitor Packaging and Labeling Processes,” and the first two sentences, “Packaging and labeling controls, critical stages in the pharmaceutical manufacturing process, are not specifically addressed in quality systems models. Therefore, the Agency recommends that manufacturers always refer to the packaging and labeling control regulations at 21 CFR 211 Subpart G,” are unambiguous English, it is very clear that this subsection only applies “to packaging and labeling” processes.</p> <p>To address the concerns raised by this commenter, improve the logical flow of the narrative, address the issue of stability-backed dating and the global issue of process/product design and development, this reviewer suggests revising this portion of the draft and the portions that follow.</p> <p>If this is done, the headings of the subsections of the “<b>C. Manufacturing Operations</b>” section will become:</p> <ol style="list-style-type: none"> <li>1. <i>Design and Develop Product and Processes</i></li> <li>2. <i>Examine Inputs</i></li> <li>3. <i>Perform and Monitor Operations</i></li> <li>4. <i>Monitor Packaging and Labeling Processes</i></li> <li>5. <i>Assess Stability and Expiration Dating</i></li> <li>6. <i>Address Nonconformities</i></li> <li>7. <i>Improve Process</i></li> </ol> <p>If the restructuring and the title revisions suggested here by this reviewer are implemented in the guidance, the text will not only be more logically structured but also address the other critical CGMP operations areas that most quality systems do not explicitly address.</p>
589, IV C.2	<p>Please add the phrase in italics: Change controls should be maintained throughout the design of the “commercial packaging” process.</p> <p>This reviewer does not agree with the commenter and suggests that the commenter’s request be ignored.</p> <p>Instead, this reviewer suggests changing the last sentence to read: “Change controls should be maintained throughout the design and design implementation process”</p>	<p>To reinforce change management is a continuum throughout the life of the product</p> <p>While this reviewer agrees that all change is a continuum, this reviewer understands that change begins at the design stage and continues throughout the life of the process and the product produced by that process. Moreover, this “change controls” statement applies globally.</p> <p>Since, conceptually, all changes are “designed” changes and then the approved design changes are implemented, the overall process is a “design and design implementation” process.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
593, IV C 3	<p>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.</p> <p>This reviewer is at a loss to comprehend how the commenter can read this text and conclude that it only applies to “raw materials.”</p> <p>However, to improve the scope this reviewer suggests revising the first paragraph to read:            “In modern quality systems models, the term <i>input</i> refers to any material that goes into a final product or is used in the manufacture, processing, or packing of the final product, no matter whether the material is purchased by the manufacturer or produced by the manufacturer for the purpose of processing. <i>Materials</i> can include items such as components (e.g., ingredients, process water, and gas), containers and closures, labels and labeling, and all packaging items and packing supplies. A robust quality system will ensure that all inputs to the manufacturing process are reliable because quality controls will have been established for the receipt, production, storage, and use of all inputs.”</p>	<p>The commenter provides no rationale for its remarks.</p> <p>Since the current first paragraph clearly states (<b>bolding</b> added for emphasis) that an “<i>input refers to any material</i> that goes into a final product,” states that “<i>Materials can include</i> items such as <b>components</b> (e.g., ingredients, process water, and gas), <b>containers, and closures,</b>” and does not even use the undefined term, “raw material,” this reviewer is at a loss to explain the comments made by this commenter here.</p> <p>The commenter’s remarks are much more confusing than the text cited.</p> <p>Nonetheless, this reviewer has revised the text to include materials “used in the manufacture, processing or packing of the final product” and provided more examples (“labels and labeling, and all packaging items and packing supplies”) so that it is even clearer that an “input refers to any material.”</p>
628, IV C 4	<p>Include change management as a separate quality system not as a paragraph under manufacturing processes.</p> <p>This reviewer does not agree with the commenter’s position and recommends that this suggestion be ignored. [<b>Note:</b> The logical, quality system, and CGMP bases for this reviewer’s position all clearly support this reviewer’s position. In addition, the FDA policies in this area seem to also support ignoring the commenter’s position.]</p>	<p>Change management should be one of the quality systems reviewed in this paper not included as a paragraph in the section on manufacturing process.</p> <p>This reviewer understands that “change management,” the commenter’s term, is an integral part of the maintenance of the process and the drug product it produces. Thus, from the “is valid” lifelong journey view of “Validation,” the control or management of change is simply one aspect of the Maintenance Qualification (MQ) phase of Validation.</p> <p>Other aspects of MQ include, but are not limited to:</p> <ol style="list-style-type: none"> <li>1. Monitoring of each:           <ol style="list-style-type: none"> <li>a. Stage of the process,</li> <li>b. Shipment lot of each incoming material,</li> <li>c. Batch or lot of in-process materials and</li> <li>d. Each batch or lot of the drug product produced by the process,</li> </ol> </li> <li>2. Ongoing acceptance or rejection of each batch or lot of finished packaged product</li> <li>3. Investigation of discrepancies, deviations, and problems,</li> <li>4. Training activities,</li> <li>5. Data tracking and trending, and</li> <li>6. Policy, procedure, and process revision.</li> </ol>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
628, IV C. 3	<p>Change “recommended” to “shall” and rearrange sentence</p> <p>This reviewer cannot agree with the commenter because:</p> <p><b>a)</b> this document is a guidance document <b>and</b></p> <p><b>b)</b> the CGMP regulations do not explicitly mandate a “change control” or “change management” system.</p> <p>Thus, while the CGMP regulations do require written procedures that control changes of all kinds, these regulations, as they should be, are not overly prescriptive – as they would be if they were to explicitly define a given system (like “change control” for compliance with the requirement minimums established therein. [Note: Just as history has seen the progression from change procedures to “change control” and thence to “change management”, hopefully, in a quality system environment, the current focus on “change management” as a somehow separate subsystem will give way, as it should, to being subsumed into one of the aspects of the more general “is valid” phase, the ongoing Maintenance Qualification phase, of “Validation.”]</p>	<p>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</p> <p>Since this document is guidance, it should not compel action <u>unless</u> that action is explicitly required by statute or the CGMP or other legally binding regulations. Factually, for example, 21 C.F.R. Sec 100(a) simply states (<b>bolding</b> added for emphasis):</p> <p><b>“§ 211.100 Written procedures; deviations.</b></p> <p><b>(a) There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.</b> Such procedures shall include all requirements in this subpart. <b>These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.”</b></p> <p>Thus, though applicable written procedures are required, the regulations do NOT explicitly require either a “change control” or a “change management” system <i>per se</i>.</p>
634, IV C 4	<p>Please state that “Perform and monitor operations” is not a quality system but a manufacturing system.</p> <p>This reviewer can “state that ‘Perform and monitor’ operations is not a quality system,” but does not agree that these are a “manufacturing system”</p> <p>However, this reviewer does recommend that the text in lines 634-642 should be revised to read:</p> <p><b>“3. Perform, Monitor, and Validate Operations</b></p> <p>The core purpose of implementing a CGMP-compliant quality systems approach is to enable a manufacturer to more efficiently and effectively perform, monitor and validate operations (21 CFR Sec. 211.110(a)). The goal of establishing, adhering to, measuring, and documenting specifications and process parameters is to objectively assess whether an operation is meeting its design (and product performance) objectives. In a robust quality system, production and process controls should be designed to ensure that the finished products have the identity, strength, quality and purity they purport or are represented to possess (CGMP also requires this; see § 211.100(a)).”</p>	<p>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?</p> <p>Apparently, this commenter failed to:</p> <p><b>a)</b> read the draft’s text carefully <b>and</b></p> <p><b>b)</b> consider that text in the context of the subject being discussed.</p> <p>In context, the topic is <b>“IV. THE QUALITY SYSTEMS MODEL, C. Manufacturing Operations, 3. Perform, Monitor and Validate Operations.”</b></p> <p>Thus, it is clear that “<i>Perform, Monitor and Validate Operations</i>,” is only one part of the <b>“Manufacturing Operations”</b> section of the <b>“QUALITY SYSTEMS MODEL”</b> being presented in this guidance.</p> <p>Based on the preceding it is clear that the commenter’s request is, at best, misplaced. However, <i>given the clear</i> “to monitor the output and <b>validate</b> the performance of those manufacturing processes ...” <i>requirements set forth in 21 C.F.R. Sec. 110(a)</i>, this section must address <b>“validate.”</b></p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
636, IV C 3	<p>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.”</p> <p>This comment should be ignored because it is, at best, inaccurate. However, this reviewer has revised that sentence (<b>see</b> the previous row) in a manner that makes it congruent with the applicable CGMP minimums that require the scientifically sound and appropriate monitoring and validating of the steps performed.</p>	<p>The core purpose is to produce a product that meets all requirements in an effective and efficient manner.</p> <p>This commenter has obviously confused the core purpose of most manufacturing systems with that of the subset of such systems that truly are quality systems oriented. Moreover, the commenter’s rationale does not properly address the clear CGMP requirement minimums set forth in 21 C.F.R. Sec. 211.110 as it must.</p>
644, IV C 4	<p>Please add in the potential role of PAT.</p> <p>This unsupported comment should be ignored by the Agency</p>	<p>The commenter provides no rationale for its remarks.</p> <p>This reviewer sees not advantage to “add in” information that is clearly only tangential the topic being discussed – the Agency has addressed PAT in other guidance which, <i>given its nature</i>, should suffice.</p>
646	<p>Change from “process weakness” to areas of “higher risk”</p> <p>This reviewer recommends that this commenter’s suggested change should be ignored because the topic being discussed in this narrative section is areas of the “process” and not areas of “risk.”</p>	<p>The concept of higher risk is consistent with this document</p> <p>Though the “concept of higher risk is consistent with this document,” the topic that is being discussed is the “process.” Since this is the case, the term “process weakness” is much more appropriate than “higher risk.” Moreover, <i>though usable</i>, the applicable “risk” term, “process risk,” is NOT appropriate because an area of process weakness may carry with it little or NO risk. [For example, a crystallization step that requires several days to complete is a “process weakness” but not, <i>per se</i>, a “process risk.”]</p>
651	<p>Change “validate” to “assess conformance”</p> <p>This reviewer rejects this suggested change because it blatantly ignores a clearly applicable CGMP requirement and, if adopted, would lead to a guidance that clearly violates the applicable CGMP minimum set forth in 21 CFR 211.110(a).</p>	<p>Assure consistency with PAT guidelines</p> <p>Since 21 C.F.R. Sec. 211.110(a) clearly states “... control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes ...” and guidance is required to conform to the clear applicable requirements of CGMP, this change should not be made. Moreover, <i>since the CGMP regulations are legally binding while guidance is not, and the commenter is supposed to know both realities</i>, this reviewer is surprised to find that those who wrote this comment would make such statements.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer's Remarks</b>	<b>Rationale &amp; Reviewer's Basis</b>
666	<p>Change "change control" to "change management"</p> <p>Again, this reviewer has no problem with the commenter's remark and could support the use of the more-general term, "Change Management," over "Change Control" <u>provided</u> the text remained fully compliant with all applicable CGMP <b>minimums</b>.</p> <p>However, as this reviewer pointed out in the comments he submitted to this docket, in reality all of the actions fall within the purview of the "Maintenance Qualification" (MQ) phase of the ongoing validation journey for each production process that begins in "Design/development Qualification" (DQ) and progresses to the MQ phase after the validity of fully function process has been established by a successful initial "Evaluation Qualification" (EQ) study.</p>	<p>Please refer to Item B in our cover letter.</p> <p>If the commenter's goal is, as it should be, to bring the terminology up to modern standards, then, a "life-long journey-based" approach that establishes that the process is valid should be adopted and changes should be addressed as integral parts of the maintenance of the qualification of the production processes and the batches of units produced by such production processes so that the process is provably valid ("validated").</p> <p>Hopefully, the Agency will revisit this portion of the draft and considers this section from the more global view of MQ, as they should.</p>

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<p>689, IV C 4</p>	<p>Please delete paragraph on using process data to improve manufacturing control.</p> <p>This obviously scientifically unsound comment should be summarily dismissed.</p> <hr/> <p>“Pharmaceutical products must meet their specifications and manufacturing processes must consistently meet their critical parameters. Under a quality system, selected data are used to evaluate the quality of a process or product. In addition, data collection can provide a means to encourage and analyze potential suggestions for improvement. A quality systems approach calls for the manufacturer to develop procedures that monitor, measure, and analyze the operations (including analytical methods and/or statistical techniques). Knowledge continues to accumulate from development through the entire commercial life of the product. Significant unanticipated variables should be detected by a well managed quality system and adjustments implemented. Procedures should be revisited as needed to refine operational design based on new knowledge. Process understanding increases with experience and helps identify the need for changes that can improve the process or the quality of the drug product. When implementing data collection procedures, consider the following:</p> <ul style="list-style-type: none"> <li>• Are the methods for the evaluation of representative samples and data collection properly documented?</li> <li>• When in the product’s production cycle will the data be collected?</li> <li>• How and to whom will measurement and monitoring activities be assigned?</li> <li>• When should analysis and evaluation (e.g. trending) of the data collected be performed (see V.E.1.)?</li> <li>• What records are needed?”</li> </ul>	<p>The idea of static process parameters – that should always be met – is not consistent with process control.</p> <p>This reviewer finds the commenter’s rationale to be flawed because, in the paragraph in question, the text does NOT propose, explicitly state, or imply the “idea of static process parameters.”</p> <p>Factually, with respect to process parameters, the paragraph in question simply states, “<b>manufacturing processes must consistently meet their parameters.</b>”</p> <p>Further, it is or should be obvious that the text makes no mention of “static parameters” – only the commenter.</p> <p>Moreover, since one of the principal requirements for “continuous improvement” is the process data alluded to in this paragraph and the commenter claims to be support “continuous improvement,” it would seem that the commenter’s request is motivated by more than the artificial “red herring” that its rhetoric has created.</p> <p>Based on the preceding, this reviewer would again suggest that the Agency should revisit its assessment of the attitudes toward CGMP compliance of those who wrote this comment because their rhetoric repeatedly seems to indicate that the commenters’ organization is not committed to operating in a manner that fully meets or exceeds all of the applicable clear CGMP <i>minimums</i> that govern this organization’s activities.</p>
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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
708	<p>Change “change control” to “change management”</p> <p>Again, this reviewer has no problem with the commenter’s remark and could support the use of the more-general term, “Change Management,” over “Change Control” <u>provided</u> the text remained fully compliant with all applicable CGMP <b>minimums</b>.</p> <p>However, as this reviewer pointed out in the comments he submitted to this docket, in reality all of the actions fall within the purview of the “Maintenance Qualification” (MQ) phase of the ongoing validation journey for each production process that begins in “Design/development Qualification” (DQ) and progresses to the MQ phase after the validity of fully function process has been established by a successful initial “Evaluation Qualification” (EQ) study.</p> <p>Hopefully, the Agency will revisit this portion of the draft and considers this section from the more global view of an integral part of the MQ phase of Validation, as they should.</p>	<p>The term change management contains the concept of inter-relatedness of process, specification, software changes in a multi-disciplinary approach.</p> <p>While the commenter’s rationale is specious, this reviewer has no problem supporting the change suggested.</p> <p>However, if the commenter’s goal is, <i>as it should be</i>, to bring the terminology up to modern standards, then, a “life-long journey-based” approach that establishes that the process is valid should be adopted and changes should be addressed as integral parts of the maintenance of the qualification of the production processes and the batches of units produced by such production processes so that the process is provably valid.</p>
725, IV C 4	<p>Please add the phrase in italics: if implemented “and operated well, will ...”</p> <p>For the factual basis reasons provided, this reviewer finds that this commenter’s request should be ignored.</p>	<p>It is necessary for the quality systems to be operated well for the statement to be correct.</p> <p>First, it is apparent that this commenter does not understand that a quality system cannot be operated. This is the case, because the quality system is the overarching set of strictures under which the unit operations covered by said quality system are operated.</p> <p>Second, this commenter seems not to understand the meaning of the verb “to implement” (which, according to the dictionary, <i>means</i> to carry into effect). Given the preceding, this comment is, at best, misguided.</p>
730	<p>Delete word “statistically” from “invalidation of test results should be scientifically and statistically sound and justified.”</p> <p>This reviewer agrees with the commenter that the word “statistically” should be deleted along with the word “and” that follows it.</p> <p>However, this reviewer finds that other changes are also needed and suggests that the sentence containing this text be changed to read:</p> <p>“Invalidation of test results should be: <b>a)</b> scientifically sound, <b>b)</b> based on an analyst error, method weakness, or equipment failure established from the critical evaluation (investigation) of all data, and <b>c)</b> justified.</p>	<p>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.</p> <p>The commenter’s rationale proverbially “strains at the gnat and swallows the camel.” The changes suggested by this reviewer reflect the reality that, in a robust CGMP-compliant quality system, conclusive proof of a cause must be found before test results can be unequivocally “invalidated.”</p> <p>Factually, since the term scientifically sound encompasses all proper uses of statistics, the phrase, “scientifically and statistically sound,” is an illogical and grammatically incorrect construction.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
734	<p>Please add in the phrase in italics: ..the manufacturer should consider shipment “and storage” requirements...</p> <p>This reviewer agrees with the commenter here.</p>	<p>Storage of pharmaceutical products can impact the quality of the products.</p> <p>This reviewer agrees with the commenter’s rationale here.</p>
737, IV.C. 4	<p>Change “continually” to “periodically” when referring to trends. Alternatively, it can be said that data should be continuously monitored for trends.</p> <p>This reviewer does not agree with the commenter here.</p>	<p>A certain amount of data is needed to identify a trend. The data must be collected over time and it is best established through continuous monitoring.</p> <p>Since processes proceed by stages, including, but not limited to, incoming, preprocess, in-process production steps, packaging, labeling, release, warehousing, and shipping, general trend monitoring is obviously restricted to an activity that can be continual but NOT continuous.</p> <p>Though the term “periodically” could be used, its “at defined intervals” connotation is at odds with the reality that trending should proceed whenever additional data is available that permits the trends being tracked to be updated or augmented.</p>
741, IV C 4	<p>Please include that ongoing process capability measurements can provide knowledge that a process is still in a validated state.</p> <p>This reviewer agrees that ongoing minimum process capability assessment can be used to support the “is valid” state for a process and suggests that the text be revised to read:</p> <p>“On-going minimum <i>process capability</i> assessment can serve as a basis for establishing that the process is still in a validated state as well as for determining the need for changes that can result in process improvements and efficiency (see IV.D.1.)”</p>	<p>The commenter provides no rationale for its remarks.</p> <p>This reviewer’s addition of the phrase “on-going minimum” addresses two realities:</p> <ol style="list-style-type: none"> <li>1. Under a CGMP-compliant QS approach, assessments are <i>on-going</i> activities, and</li> <li>2. To be both <i>scientifically sound</i> and <i>CGMP-compliant</i>, the <i>process capability</i> approach must address the <i>minimum capability</i> of the process.</li> </ol> <p>[Note: The basis for the inclusion of the commenter’s phrase, “is still in a validated state,” is that, <i>as long as the minimum process capability values calculated for all of the critical variable characteristics in the process are both stable and exceed their predetermined “process is valid” minimums</i>, the process can be considered to be valid.]</p>
767, IV C 5	<p>Please define the “proper authorization”</p> <p>This reviewer sees no need to define “proper authorization” because this guidance is intended for use by firms that are regulated by the CGMP regulations for finished pharmaceuticals.</p>	<p>It is necessary to clarify if it is an external or internal authority.</p> <p>Since the CGMP regulations clearly place the authority for all release decisions with the “quality control unit” (see §§ 211.22(a) and 211.115(b)), only the “quality control unit” can provide “proper authorization.”</p> <p>Thus, the commenter’s stated rationale indicates that some of the commenter’s personnel again seem to lack the requisite “education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions” (§ 211.25(a)).</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
769, IV C. 5	<p>Change the term “can” or “should” or “must” or insert language such as “a recall should be considered”</p> <p>Considering the commenter’s change suggestions and recognizing the validity of the commenter’s rationale, this reviewer recommends changing the draft to read:</p> <p>“If an individual product that does not meet requirements has been released, the Agency must be notified “immediately”<sup>19</sup>, and the product should be recalled.”</p>	<p>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.</p> <p>Because this document is a guidance document, it must advise as to what a firm “must” do when a requirement issue, such as notification, is raised. Conversely, given that recall is a voluntary activity, “should” is the proper word that should be used. Should the Agency disagree with a firm’s decision in such cases, the Agency can initiate other corrective actions.</p>
770, IV C. 5	<p>Change “Customer complaints should...” to “Quality related customer complaints should be handled as potential discrepancies....”</p> <p>This reviewer knows that this comment should be ignored.</p>	<p>The commenter provides no rationale for its remarks.</p> <p>Under a quality system, all customer complaints should be treated as discrepancies as well as investigated, under CGMP, if they bear on a quality issue. Moreover, the applicable CGMP regulations require a written justification for any decision not to investigate.</p>
790, IV D 1	<p>“Analysis of data can provide” suggest “Analysis of data can provide an indication of the state of control of a process.”</p> <p>This reviewer agrees with the commenter’s suggestion and suggests revision the text to read:</p> <p>“Analysis of data can provide indications <del>that controls are losing effectiveness</del> of the state of control of a process.”</p> <p>In addition the verb “will” in the next sentence should be changed to “may” to reflect reality.</p>	<p>The commenter provides no rationale for its remarks.</p> <p>Since the original text, “indications that controls are losing effectiveness,” is but one facet of the indications that an analysis of the data can generate, the commenter’s proposed “indications of the state of control of a process” is a better wording choice in this instance.</p> <p>Factually, outcomes may or may not provide the information suggested so that the use of the verb “will” is not appropriate here.</p>
794, IV D.1	<p>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</p> <p>This reviewer recommends that this comment be ignored.</p>	<p>Data in these cases in insufficient to detect significant trend.</p> <p>As it is equally true that high volume products may generate data at rates that permit daily trending and, <i>in “low volume” processes</i>, increasing the number of units evaluated can be used to compensate for “low volume,” this reviewer recommends keeping the current “regular basis” wording since, <i>because this is a guidance document</i>, the current wording clearly allows the adopter to define “regular basis” in whatever manner it wishes <u>provided</u> the frequencies set are justified by the production rates for the drug product for which they have been defined.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
808, IVD2	<p>An annual audit of entire quality system may not be achievable.</p> <p>This reviewer rejects this commenter’s indefinite statement, “... may not be ...” because, without a periodic, comprehensive, <i>at least annual</i>, audit of the firm’s entire quality system, the firm cannot KNOW that it has a truly valid quality system.</p>	<p>It is logistically impossible and not value added to audit the entire quality systems. Elements of the system should be reviewed annually.</p> <p>Unless a firm is able to audit its entire quality system on an ongoing basis so that, <i>at least annually</i>, all of its operational units have been audited, that firm does not truly have a valid quality system for that firm and it cannot validly assess the overall quality system it has implemented.</p> <p>This does not mean that once a year the firm should stop and audit everything – a full audit can be achieved by auditing defined portions of the firms operational activities in e.g., the first 11 months of a year and reserving the last month for a review of and report on the global quality system for that firm.</p>
824, IV D	<p>Please add in the phrase in italics: Understanding of quality issues “and their risk to patients”</p> <p>This reviewer does not support the commenter’s request here and recommends that it be ignored.</p>	<p>Addition of risk to patients is consistent with a risk based model for GMPS (sic)</p> <p>First of all, since “risk to patients” is a quality issue, there is absolutely no need to add it as the commenter requests.</p> <p>Second, as far as this reviewer knows, there is NO “risk based model for GMPS (sic)”</p> <p>Third, as far as this reviewer knows, “GMPS” is not an Agency-recognized acronym – the pertinent proper FDA-recognized acronyms are “CGMP,” the proper acronym for the 4-word phrase, “current good manufacturing practice,” and “GMP’s,” the narrowly applicable (<b>see</b> 21 C.F.R. § 26.3) acronym for the phrase, “Good Manufacturing Practices,” which is defined in § 26.1(c).</p>
840, IV D 4	<p>Please change from “Corrective Action” to “Preventive Action”</p> <p>This reviewer knows that the commenter’s request should simply be ignored.</p>	<p>This section describes Preventive actions not corrective actions.</p> <p>Since the commenter’s understanding of CAPA and of what constitutes “Corrective Action” are flawed and the section clearly describes corrective actions triggered by event occurrences, the commenter’s remarks should simply be dismissed.</p>
890, V	<p>Remove delete sentence “Quality professionals are aware that good intentions alone..”</p> <p>This reviewer agrees with the commenter in this instance.</p>	<p>The sentence is not value added.</p> <p>This reviewer supports the commenter’s rationale here – the sentence in question adds no value to the topic being discussed.</p>
895, V	<p>Please add in a summary bullet describing change management.</p> <p>This reviewer does not support the commenter’s ill-conceived request.</p>	<p>Change management is an essential function of a quality system and is discussed in detail</p> <p>Change management, though an essential function (like sampling and data acquisition), is a subsidiary function that does not belong in this bulleted list.</p>

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**C-03 Comments By Aventis Pharmaceuticals, Posted 30 November 2004**

Aventis begins by stating:

“Aventis Pharmaceuticals appreciates the opportunity to comment on the above-referenced Draft Guidance entitled “*Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*”.

This draft guidance describes the key elements of a robust quality systems model and shows how persons implementing such a model can achieve compliance with the CGMP regulations.

In general, the guidance draft provides a good summary and is to be applauded.”

Aventis’ reviewed comments are as follows:

**SPECIFIC COMMENTS**

**II. BACKGROUND AND PURPOSE**

**B. Goal of the Guidance**

**Lines 98-103:** *The FDA has concluded that modern quality systems, when coupled with manufacturing process and product knowledge, can handle many types of changes to facilities, equipment, and processes without the need for a 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. In addition, an effective quality system, by lowering the risk of manufacturing problems, may result in shorter and fewer FDA inspections.*

Aventis request further clarification regarding the statement on the ability to implement changes without prior approval. We suggest defining some examples for changes without prior approval, e.g. in an appendix.

While the commenter’s boxed text is artfully constructed, it overlooks the reality that US statutes and binding FDA regulations establish the limits on the allowable “regulatory flexibility” and not the quality system or how it is implemented.

In addition, since there are FDA documents that directly address changes and the rules governing them, the commenter should address its requests and suggestions to these documents and not to this guidance.

Furthermore, *when an organization has truly implemented a robust CGMP-compliant quality system that builds quality into its processes and products*, that firm’s original submissions should contain all of the established “flexibilities” (required to handle the worst-case permissible variations in the incoming and in-process materials and the processing steps) that are required to ensure that the final drug product still meets the predetermined quality expectations (criteria for acceptance for release) established in the firm’s submission documents.

Based on the preceding realities, the Agency should ignore this request because it is not germane to the guidance issues being addressed.

**Lines 118-119:** *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.*

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This text gives rise to the expectation that employing a quality system according to this guideline will lead to relief regarding inspections and regulatory burden. This is very positive. However we request further clarification of this statement and suggest that FDA provides tangible examples.

First of all, the quoted text, **Lines 118-119**, does not address Aventis’ stated “expectation that employing a quality system according to this guideline will lead to relief regarding inspections and regulatory burden.”

Second of all, since the draft document is not a guideline, it does not, as a true guideline would, bind either the Agency or the commenter to any set course of action, as the commenter’s knowing misuse of the word “guideline” seems intended to do.

Third, since the document is only guidance, it cannot bind the commenter to any course of action – with respect to those areas addressed by this guidance document, the commenter is only bound to follow those courses of action that it has elected in writing to follow in a manner that fully complies with CGMP as that term is used in 21 U.S.C. Sec. 351(a)(2)(B) including the *minimums* clearly set forth in the applicable CGMP regulations as well as with any other legally binding regulations to which the commenter’s self-imposed directives in this area are impacted.

Since these are the case, this reviewer is at a loss to see how the Agency can clarify, or that it should even attempt to clarify, the statement cited in the manner requested by this commenter.

In addition, this reviewer again finds the commenter’s repeated request for “examples” to be a request that should be directed to those FDA documents whose scope includes the issues this commenter again raises.

**C. Scope of the Guidance**

**Lines 115-116:** *It may also be useful to manufacturers of components used in the manufacture of these products.*

We request clarification on whether this applies to API manufacturers. As the sentence is written the language indicates that there is no difference seen between the API, excipients, process support materials (e.g. Nitrogen), and primary or secondary packaging.

Since APIs are components, it should be **obvious** that this statement applies to “API manufacturers” because each “API” is, *by definition* (see 21 U.S.C. Sec. 321(g)(1)(D)), a component of a drug and, *under that definition*, components of a drug are drugs.

Thus, the draft guidance here should be left as it is because it clearly and appropriately defines the scope of this guidance and, because API’s are “components” permits “API manufacturers” to use it if they find it “useful.”

Based on the preceding, the commenter’s suggestion should be ignored.

**III. CGMPs AND THE CONCEPTS OF MODERN QUALITY SYSTEMS**

**F. The Quality Unit**

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**Lines 234-235:** *Under a robust quality system, the manufacturing units and the quality unit can remain independent, but still be included in the total concept of producing quality products.*

We request further clarification on what is meant by “*manufacturing units and the quality unit can remain independent*”? What would be the preferred alternative?

Since the guidance does not suggest, by using a “should,” a preference, the commenter is free to adopt whatever arrangement it chooses as long as that arrangement meets the statutory expectations of CGMP and the **minimums** set forth in the applicable CGMP regulations.

Since the CGMP regulations clearly require a separate quality control unit with several explicit responsibilities (**see**, for example, 21 C.F.R. Sections 211.22(a)), 211.22(c), 211.42(c)(1), 211.84(a), 211.87, 211.100(a), 211.101(c)(1), 211.110(c), 211.115(b), 211.142(a), 211.160(a), 211.165(d), and 211.198(a)) as well as two explicit authorities, the “authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated” (**see** 21 C. F. R. Sec 211.22(a)), these regulations define the **minimum acceptable** arrangement that a firm can legally adopt.

Alternatively, provided it continues to meeting all of the applicable CGMP minimums, a firm may validly choose to use a slightly more rigorous quality assurance unit approach (as defined in 21 C.F.R. Sec. 58.3(l)) in which, by analogy, the firm’s “quality unit” would be “entirely separate from and independent of the personnel engaged in the direction and conduct of” (21 C.F.R. Sec. 58.35(a)) all operational activities.

Finally, provided it meets all of the applicable CGMP minimums, a firm may validly elect to give its quality unit the final decision authority over all aspects of its activities, though this reviewer would be surprised if any firm were to choose this option.

Hopefully, the preceding has addressed all of the viable CGMP-compliant alternatives and reinforced the reality that the option a firm makes is up to the firm making the choice.

All that the FDA can legally and should require is that, an FDA-regulated drug-products firm must remain fully CGMP compliant *in whatever practices said firm elects or purports to implement*.

Moreover, *as the commenter should know and the US Supreme Court has ruled*, even if the Agency apparently does not actively enforce all of the requisite standards, a regulated firm may not use the Agency’s inaction as a defense for that firm’s knowing failure to comply with any legally binding statute or regulation.

#### **IV. THE QUALITY SYSTEMS MODEL**

##### **C. Manufacturing Operations 1. Design and Develop Product and Processes**

**Lines 543-547:** *In a modern quality systems manufacturing environment, the significant characteristics of the product being manufactured should be defined, from design to delivery, and control should be exercised over all changes. Quality and manufacturing processes and*

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*procedures — and changes to them — should be defined, approved, and controlled (CGMP also requires this; see § 211.100).*

We suggest including development, not only design, for addressing pharmaceutical manufacturing.

In this passage, this reviewer sees no need to include “development,”

This is the case because the phrase in question, “*from design to delivery*,” is intended to indicate the beginning and ending of the quality system’s scope of coverage.

Therefore, this reviewer would recommend that the Agency ignore simply this suggestion.

**C. Manufacturing Operations 4. Perform and Monitor Operations**

**Lines 652-654:** *In a quality system, process validation provides initial proof, through commercial batch manufacture, that the design of the process produces the intended product quality.*

This text indicates that prospective process validation is always necessary prior to marketing. This conflicts with the new validation policy guide and therefore, Aventis recommends adapting the text to the validation policy guide. We also requests clarification that new technology and manufacturing science application can eliminate the need for conformance batches prior to marketing.

First, this reviewer finds that the passage quoted has been artfully taken out of context.

Second, the statement cited does not state or imply, per se, “that prospective process validation is always necessary prior to marketing” all that the text passage does state is that, “*(i)n a quality system, process validation provides initial proof, through commercial batch manufacture, that the design of the process produces the intended product quality – a very different statement.*

Third, when put back into its context (**bolding added**),

“In a modern quality system, a design concept established during product development typically matures into a commercial design after process experimentation and progressive modification. Areas of process weakness should be identified, and factors that are influential on critical quality attributes should receive increased scrutiny. (The FDA recommends that scale-up studies be used to help demonstrate that a fundamentally sound *design* has been fully realized.) A sufficiently robust manufacturing process should be in place prior to commercial production. With proper design (see section IV.C.1), and reliable mechanisms to transfer process knowledge from development to commercial production, a manufacturer should be able to validate the manufacturing process.<sup>14</sup> **In a quality system, process validation provides initial proof, through commercial batch manufacture, that the design of the process produces the intended product quality.** Sufficient testing data will provide essential information on performance of the new process, as well as a mechanism for continuous improvement. Modern equipment with the potential for continuous monitoring and control can further enhance this knowledge

<sup>14</sup> See Reference #6.

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base. Although initial commercial batches can provide evidence to support the validity and consistency of the process,<sup>15</sup> the ~~entire life cycle~~ ongoing production should be addressed by the establishment of continuous improvement mechanisms in the quality system.<sup>16</sup> Thus, in accordance with the quality systems approach, process validation is not a one time event, but an activity that continues.”

this reviewer finds no obvious conflict between this guidance and the Agency’s “new validation policy guide” (i.e., FDA Compliance Policy Guide 7132c.08, “Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval,” updated 03-12-2004).

That being said, this reviewer finds the commenter’s recommendation seems to be baseless on its face.

Further, with respect to the commenter’s request, “We also requests clarification that new technology and manufacturing science application can eliminate the need for conformance batches prior to marketing,” besides being grammatically incorrect, to be a request that falls outside of not only the scope and intent of this guidance bit also is outside of the general scope of the quality systems approach to drug production systems.

Since, *under the Agency’s “new validation policy guide”*:

- a. All batches are validation batches because each batch serves to establish that the process is valid, and
  - b. A process must be initially validated (determined to be valid) before a sponsor’s application may be approved,
- it also seems that the commenter’s request is itself at odds with the Agency’s “new validation policy guide.”

**Lines 677:** *Process steps should be verified using a validated computer system or a second person.*

We suggest adding “critical” as the first word of the sentence since only “critical process steps” should be monitored with a second signature.

Since this commenter provides no supporting rationale for its statement and, when one uses a quality systems approach, one must verify the performance of all steps, this reviewer suggests that this comment should be ignored.

Moreover, from a quality systems viewpoint, the only steps that are NOT “critical” are those that can and should be deleted from the operational system because they are absolutely unnecessary.

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<sup>15</sup> Even with good design and development work, initial *conformance batches* only provide confidence that future batches will meet specifications if the process is repeated within defined operating parameters, equipment tolerances, personnel practices, environmental attributes, and material quality.

<sup>16</sup> See Reference #7.

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**C-04 Comments By Computer Systems Services & Consulting, Inc. ("CSSC"),  
Posted 30 November 2004**

CSSC begins by stating:

**"Summary**

CSSC, Inc. feels that the expectations described in the draft Guidance for Industry mirror existing quality system requirements in 21 CFR 820, and we propose establishing clearer links between the existing regulation and the new Guidance. CSSC is concerned that a Quality System Guidance that is not linked to predicate regulations could potentially confuse firms attempting to comply with interdivisional expectations.

**Introduction**

In September 2004, FDA issued a draft guidance document whose stated purpose is to "help manufacturers that are implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practices (CGMP) regulations," specifically as described in 21 CFR Parts 210 and 211.

This draft document solicits input from industry.

CSSC, Inc. is a worldwide regulatory and compliance consulting firm headquartered in Morristown, N.J. CSSC specializes in assisting pharmaceutical firms in meeting FDA compliance expectations, especially those involving Quality Systems and Good Manufacturing Practices. In response to an emphasis placed on Quality Systems inspections by FDA's New Jersey District Office, CSSC has increased its expertise in this field by recruiting managers with strong backgrounds in Medical Devices Quality Systems—the ISO13485 standard and especially 21 CFR 820, the Quality System Regulation (QSR). CSSC therefore is providing comment on the draft Guidance as a representative consultant to the pharmaceutical industry."

As the text that follows, it should become crystal clear, *to any who understand drug and finished pharmaceutical CGMP*, that this commenter seems to be somewhat deficient in its understanding of these areas as its "involving Quality Systems and Good Manufacturing Practices" statement clearly indicates. [Note: 21 CFR Sec. 820.1(a)(1) clearly states that "Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation" – not that Good Manufacturing Practices (GMP) ...].

That having been stated, let us proceed to review the commenter's remarks.

CSSC's reviewed comments are as follows:

**"The QSR and QSIT**

The Quality System Inspection Technique, or QSIT, is an internal FDA document developed by the Center for Devices and Radiological Health (CDRH) to facilitate inspections of Medical Device firms. It directs Consumer Safety Officers and other Agency Inspectors to concentrate on a select sample of subsystems whose impact on product quality and regulatory compliance is well established. QSIT is not itself a law, regulation, or guidance; but it is predicated on quality concepts practiced throughout the industry and which are a subset of the expectations spelled out in CDRH's *Medical Device Quality System Manual: A Small Entity Compliance Guide*.

As stated, QSIT (and the QSR it supports) applies only to the Medical Device industry.

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However, FDA has a long-standing policy of applying any division’s rules to wherever it may be pertinent to assuring the public health. For example, another CDRH document, *Guidance for Industry: General Principles of Software Validation* has found widespread application throughout the regulated Life Sciences industry. Furthermore, the Quality System Regulation contains an implicit statement that its scope far exceeds just Medical Devices: ‘The quality system regulation in this part supplements regulations in other parts of this chapter except where explicitly stated otherwise’ (21 CFR 820.1(b)).”

Given the text quoted from 21 C.F.R. Part 820, it is clear that the Part 820 only “supplements,” not replaces or supersedes, “the regulations in other parts of this chapter ...” (21 CFR 820.1(b))

Moreover, this reviewer notes that this commenter has misquoted 21 C.F.R. Sec. 820.1(b) (which actually states: “Limitations. The quality system regulation in this part supplements regulations in other parts of this chapter except where explicitly stated otherwise. In the event that it is impossible to comply with all applicable regulations, both in this part and in other parts of this chapter, the regulations specifically applicable to the device in question shall supersede any other generally applicable requirements”) by leaving out the first statement “Limitations.”

Hopefully, this commenter and the Agency will remember this reality as should.

“It is therefore clear that drug firms are already subject to quality system requirements.”

Contrary to the commenter’s remarks here, it is: **a)** not clear that the “drug firms are subject to the finished-device quality system requirements” and **b)** also not true.

First, this is the case because the text of (21 CFR 820.1(b)) does not include either the word “supersedes” or the wording like “in the event it is impossible to comply with applicable regulations both in this part and in other parts of this chapter, the regulation in question this part shall supersede the regulation in that other part or parts.”

Second, the current language of the 21 CFR Part 210 contains the following “Status” and “Applicability” text:

“§ 210.1 Status of current good manufacturing practice regulations.

(a) The regulations set forth in this part and in parts 211 through 226 of this chapter contain the minimum current good manufacturing practice for methods to be used in, and the facilities or controls to be used for, the manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.

(b) The failure to comply with any regulation set forth in this part and in parts 211 through 226 of this chapter in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

§ 210.2 Applicability of current good manufacturing practice regulations.

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(a) The regulations in this part and in parts 211 through 226 of this chapter as they may pertain to a drug and in parts 600 through 680 of this chapter as they may pertain to a biological product for human use, shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the drug in question shall supersede the more general.

(b) If a person engages in only some operations subject to the regulations in this part and in parts 211 through 226 and parts 600 through 680 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.”

Similarly, the current language of the 21 CFR Part 211 contains the following “Scope” text:

“§ 211.1 Scope.

(a) The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals.

(b) The current good manufacturing practice regulations in this chapter, as they pertain to drug products, and in parts 600 through 680 of this chapter, as they pertain to biological products for human use, shall be considered to supplement, not supersede, the regulations in this part unless the regulations explicitly provide otherwise. In the event it is impossible to comply with applicable regulations both in this part and in other parts of this chapter or in parts 600 through 680 of this chapter, the regulation specifically applicable to the drug product in question shall supersede the regulation in this part.

(c) Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this part shall not be enforced for OTC drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use. Therefore, until further notice, regulations under part 110 of this chapter, and where applicable, parts 113 to 129 of this chapter, shall be applied in determining whether these OTC drug products that are also foods are manufactured, processed, packed, or held under current good manufacturing practice.”

Thus, any failure to comply with any of the clear CGMP requirements set forth in 21 CFR Parts 210 and 211 renders the product produced an adulterated product.

Hopefully, after carefully reading the cited passages, the commenter understands the reality.

“While the draft guidance intimates this in Section I (“This guidance is not intended to place new expectations on manufacturers”), it never states clearly that firms have a pre-existing obligation to meet quality system expectations. A firm could therefore erroneously conclude that maintenance of a compliant quality system is entirely optional.”

Given the following realities:

- a. 21 C.F.R. Parts 210 and 211, including the amendments that become effective in May of 2005, does not explicitly address 21 C.F.R. Part 820 in any direct manner,
- b. the only sections of 21 C.F.R. 820 that may supplement 21 CFR Parts 210 and 211 are those that, as written, do not specifically address a device, and

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c. the fact that all that is **required** of a drug product firm is for that firm to fully comply with the applicable portions of 21 C.F.R. Parts 210 and 211 and the general statutory expectations of 21 U.S.C. Sec. 351(a)(2)(B), this reviewer finds a drug firm could “conclude that maintenance of a compliant quality system is entirely optional.”

Further, had the Agency wished to require drug firms to maintain a quality system for drugs, like they have for devices, then the Agency would have simply revised 21 CFR Parts 210 and 211 appropriately.

Obviously, the Agency not only did not take that course of action but also has issued this draft guidance, “**Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations.**”

Thus, this reviewer must conclude that this commenter’s position is not correct.

“CSSC has performed an analysis of the individual quality elements contained in the draft guidance and compared them to 21 CFR 820. With the notable exception of Laboratory Controls-which do not have dedicated requirements in the current draft-every element maps directly to specific and *preexisting* expectations in the Quality System Regulation, as shown in the following table:”

Since 21 CFR Part 820 is a “quality system regulation” for devices, any quality system guidance should be able to be mapped onto this guidance.

Thus, this reviewer would have been surprised if this were not the case.

Further, this commenter should have excluded those sections that are explicitly or indirectly meant only for devices from its table.

When this is done, there are very few *preexisting* expectations that may, *but (as the regulations for drugs are written) are not, per se, required to*, be applied to drug products, the “Quality Systems Approach” area addressed in this guidance.

In addition, this commenter seemed to misplace sections of 21 C.F.R. Part 820 in some cases.

The table that follows is reflects the entries that remain after the corrections suggested by this reviewer are made.

<b>Draft Guidance Element</b>	<b>Corresponding Usable QSR</b>	<b>Draft Guidance Element</b>	<b>Corresponding Usable QSR</b>
Quality by Design	820.20(d)	Purchasing Controls (Outsourced Operations)	Most of 820.50
<b>Risk Analysis and Management</b>		<b>Process Design</b>	
Resource Management	“820.25(a)” [Dup. in 211]	Packaging and Labeling Control	“820.40” [Doc. Control], “820.120” [Dup. in 211]
Change Control	“820.40” [Doc. Control], “820.70(b)” [Dup.in 211]	<b>Input Requirements</b>	
<b>The Quality Unit (quality management)</b>		<b>Output Verifications</b>	
<b>Defined Management Responsibilities</b>		Process Monitoring (process control)	820.75(b)
<b>Organizational Structure</b>		Nonconformity Processes	“820.90” [Dup. in 211]
Quality Policies	820.20(a)	Continuous Improvement	
<b>Quality System Review</b>		Internal Audits	820.22
CAPA	Most of 820.100	Trend Analysis	Part of 820.100(a)(1) 820.250(a)

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Thus, the commenter's original table seem to have been, at best, overly zealous.

"Laboratory Controls are difficult to map into Part 820, which expects quality processes to be applied upon applicability and risk, rather than regulatory demarcations such as those found in 21 CFR 211.160 or Part 58. Nonetheless, the draft guidance does not appear to assign Laboratory Controls special status but instead reminds users that laboratories should be subject to the same quality expectations as other areas and functions."

This reviewer recognizes that the commenter's statements are derived from their misunderstanding of 21 C.F.R. Sec 211.160.

Though 21 C.F.R. Sec 211.160 is the first section in "Subpart I—Laboratory Controls," persons who truly understand the CGMP regulations for finished pharmaceuticals know that "Sec. 160 General Requirements" establishes the controls for all operations that bear upon the manufacture, processing, packing or holding of the finished drug product. [Note: This commenter is urged to read this reviewer's comments to this docket if it wishes to verify the validity of this reviewer's statement here.]

Since this commenter obviously lacks the requisite knowledge and understanding, it is not surprising that the reviewer mistakenly identifies the requirements set forth in "Sec. 160 General Requirements" as controls for the laboratory.

Hopefully, after reading this reviewer's remarks, this commenter will revisit 21 C.F.R. Sec. 211.160 and carefully study its requirements and the scope of their coverage.

"In some cases, references have been made in this table to the Medical Device Design Control requirements. CSSC does not infer that drug manufacturers are, or should be, subject to 21 CFR 820.30; we recognize that the development of pharmaceuticals is substantially different than devices. However, it is axiomatic that the concepts behind design controls (as embodied by more general standards such as ISO9001) are vital to successful quality implementation. The concepts of documented design inputs, verified outputs, and management review and oversight have applicability across the entire quality system, and the draft guidance appears to embrace these widely accepted precepts."

This reviewer finds that, while the commenter at least recognizes ("CSSC does not infer that drug manufacturers are, or should be, subject to 21 CFR 820.30") that parts of 21 C.F.R. Part 820 do not apply to drug manufacturers, the rest of the comments made here add little of substance to the subject of this guidance.

**Conclusion**

Since it can be demonstrated that the elements of the proposed guidance map into Part 820—an existing regulation widely viewed as the premier quality standard in the Life Sciences—CSSC questions the approach taken in presenting essentially the same elements in a different format. We are concerned that this could result in confusion in the industry as to what standard to utilize, especially for firms engaged in production of Combination Devices."

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Since the commenter's "mapping" premise is incompletely supported, this reviewer finds that the commenter's first statement is at odds with reality and that it should therefore be ignored.

Since this commenter has a confused and incomplete understanding of the CGMP regulations for drugs (Part 210) and finished pharmaceuticals (Part 211), this reviewer can easily see that this commenter would be "concerned that this could result in confusion in the industry as to what standard to utilize, especially for firms engaged in production of Combination Devices"

However, this reviewer is concerned about consultants who seem not to meet the CGMP requirements set forth in 21 C.F.R. 211.34:

"Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide."

"CSSC therefore respectfully requests that the Agency modify the draft Guidance for Industry: Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations to explicitly cite 21 CFR Part 820 as an underlying structure and reorganize the elements to match those already found in The Quality System Inspection Technique, along with those additional Part 211-specific elements that are unique to drug and biologics manufacturers (for example, the explicit requirement for and duties of a dedicated Quality Control Unit under 21 CR 211.22). This way, firms will have a clear understanding of Agency expectations of their Quality System, regardless of whether they are audited by CDER, CDRH, or their local district office."

Based on this commenter's demonstrated lack of understanding of 21 CFR Parts 210 and 211 and the other instances where the commenter seems to have made statements that, to varying degrees, seem to diverge from factual reality, this reviewer respectfully requests that the Agency ignore this commenter's request and proceed to appropriately revise and issue this basically well-written guidance.

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**C-05 Comments By Aventis Pasteur, Posted 3 December 2004**

Aventis Pasteur begins by stating:

“Aventis Pasteur Inc. of Swiftwater, Pennsylvania thanks the Food and Drug Administration (FDA) for the opportunity to comment on the above-referenced draft guidance for industry entitled, “Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations.” Aventis Pasteur Inc. is part of the Aventis Pasteur family of companies, which consists of the parent firm Aventis Pasteur SA, headquartered in Lyon, France, Aventis Pasteur Inc., and other subsidiaries (collectively Aventis Pasteur). In turn, Aventis Pasteur SA is a subsidiary of Aventis SA.

Aventis Pasteur is a world leader in vaccines and produces more than one billion doses of vaccines every year to immunize 400 million people around the world. Aventis Pasteur, in close consultation with the US public health establishment, including the FDA, and Centers for Disease Control and Prevention (CDC), strives to alleviate the suffering and death of vaccine-preventable diseases.

We offer the following comments for your consideration concerning the FDA's solicitation of responses as they apply to the Biologics (Vaccine) industry.

**General Comment**

The majority of the guidance document provides a high level assessment of what a quality unit must contain, the responsibilities of management in establishing quality systems, and the function of the quality system. The guidance document also reflects its ISO influence concerning the criticality of the role of management in the quality process.”

Aventis Pasteur's reviewed comments are as follows:

**“Specific Comments**

Aventis Pasteur agrees with the basic concepts of the guidance document, as well as the philosophy expressed in Lines 81 and 82:

*Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.*

While this reviewer generally agrees with the commenter here, this reviewer would again suggest that the text in question be revised to read:

***“Quality must be built into the product, the critical variable characteristics for all inputs must be adequately controlled, and, though required by CGMP, representative-sample testing alone cannot be relied on to ensure product quality.”***

Because the CGMP regulations establish requirement *minimums* that explicitly address product quality, quality **must** be built into all drug products.

In addition both the CGMP regulations and most quality systems recognize that, *in general*, the critical variable characteristics of all inputs must be controlled before the quality of the output can be ensured.

Finally, *unless population-representative samples are tested*, a manufacturer **cannot** validly assess the quality of each lot or batch of the finished products that the firm manufactures, processes, packs, or holds.

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Thus, the text should be revised as this reviewer suggests if, as they should be, the fundamental quality premises set forth in the original text are to be aligned with the quality **minimums** set forth in the applicable CGMP regulations contained in 21 C.F.R. Parts 210 and 211.

“In Lines 98-103 the document states:

*The FDA has concluded that modern quality systems, when coupled with manufacturing process and product knowledge, can handle many types of changes to facilities, equipment, and processes without the need for a 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. In addition, an effective quality system, by lowering the risk of manufacturing problems, may result in shorter and fewer FDA inspections.*

Aventis Pasteur notes that FDA has made some broad and powerful statements in this passage regarding changes that can be made to facilities, equipment and processes without the requirement of a prior regulatory filing. As this statement is so broad, it would be beneficial if FDA could provide some specific circumstances or examples in which a regulatory filing would not be required.”

While the commenter's request is artfully constructed, it overlooks the reality that US statutes and binding FDA regulations establish the limits on the allowable “regulatory flexibility” and not the quality system or how it is implemented.

In addition, since there are FDA documents that directly address changes and the rules governing them, the commenter should address its requests and suggestions to these documents and not to this guidance.

Based on the preceding realities, the Agency should ignore this request because it is not germane to the guidance issues being addressed.

“The guidance document indicates there will be a six-system inspection model (begins Line 239), with the Quality System being the main focus. However, little information is provided on the other five systems: Materials System, Laboratory Controls System, Facilities and Equipment System, Production System, and Packaging and Labeling System. It would be beneficial to make more specific information available on these systems, as well as on management of information and computer systems.”

Since the issues raised by this commenter here are outside the scope of this guidance, this reviewer recommends that the Agency consider issuing additional guidance in the inspection area or otherwise address the commenter's concerns outside of this guidance and that the commenter carefully review the FDA's internal “The Quality System Inspection Technique” (QSIT) document and all of the documents appertaining thereto.

Moreover, this reviewer does not recommend addressing the areas suggested by the commenter in this guidance document.

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**C-06 Comments By PDA, Posted 3 December 2004**

The PDA begins by stating:

“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:”

Before beginning the review, this reviewer would like to thank the Agency personnel in the Division of Dockets Management for posting this commenter's remarks to the correct docket, “2004D-0443,” and not to the docket to which the PDA submitted said comments, “submitted to Docket # **2004D-0043 CDER 2004 115.**”

PDA's reviewed comments are as follows:

**Review of 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.”

Sadly, this reviewer notes that the commenter seems to have either misunderstood what the text is saying or deliberately twisted the message in the cited passage to suit the commenter's purposes.

Factually, the cited text states, “With the globalization of pharmaceutical manufacturing and the increasing prevalence of drug- and biologic-device combination products, the convergence of quality management principles across different regions and among various product types is very desirable.”

Thus, all that the FDA is doing is recognizing: **a)** two existent trends (“globalization of pharmaceutical manufacturing” and “increasing prevalence of ... combination products”) **and b)** “the convergence of quality management principles across different regions and among various product types is very desirable.”

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Plainly, all the FDA is recognizing is the applicable “quality management principles,” *that are already recognized globally (in the “ISO 9000” series of standards, ISO/IEC 17025, and other such standards)*, can easily be applied to the drug and finished pharmaceutical CGMP regulations through the simple “Quality System Model” proposed in this guidance.

Accurately, the FDA has already formally recognized, in 21 C.F.R. “PART 26—MUTUAL RECOGNITION OF PHARMACEUTICAL GOOD MANUFACTURING PRACTICE REPORTS, MEDICAL DEVICE QUALITY SYSTEM AUDIT REPORTS, AND CERTAIN MEDICAL DEVICE PRODUCT EVALUATION REPORTS: UNITED STATES AND THE EUROPEAN COMMUNITY,” that the quality systems used by the U.S. and the European Community cannot be harmonized because of fundamental differences in the basis definition of what constitutes compliance (21 CFR 26.1(c), “Good Manufacturing Practices (GMP's). [The United States has clarified its interpretation that under the MRA, paragraph (c)(1) of this section has to be understood as the U.S. definition and paragraph (c)(2) as the EC definition.]

(1) GMP's mean the requirements found in the legislations, regulations, and administrative provisions for methods to be used in, and the facilities or controls to be used for, the manufacturing, processing, packing, and/or holding of a drug to assure that such drug meets the requirements as to safety, and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess.

(2) GMP's are that part of quality assurance which ensures that products are consistently produced and controlled to quality standards.

For the purpose of this subpart, GMP's include, therefore, the system whereby the manufacturer receives the specifications of the product and/or process from the marketing authorization/product authorization or license holder or applicant and ensures the product is made in compliance with its specifications (qualified person certification in the EC).”).

Thus, instead of seeking to “harmonize quality systems,” the Agency has recognized that, as it should, the time is right for the Agency to forth the FDA's current view of a Quality System Model that, *if properly implemented*, can be used in a CGMP-compliant environment.

**“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.”

This reviewer again finds that the commenter's statements knowingly diverge from what the guidance states when it confuses “less strict regulatory submissions” with the guidance's statement concerning “... changes to facilities, equipment, and processes without the need for a regulatory submission.”

The guidance here speaks to “fewer” submissions and not the commenter's “less strict regulatory submissions.”

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Based on the preceding, the Agency should simply ignore this commenter’s remarks here.

**“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.”

This reviewer suggests that the commenter’s recommendation, “that API and bulk biologic manufacturing be considered for inclusion in the list of the types of manufacturers affected by this guidance,” should be considered in a separate guidance so that the issues unique to such **components** of “finished pharmaceuticals” could be properly addressed.

Moreover, because the guidance continues by stating, “It may also be useful to manufacturers of components used in the manufacture of these products,” and APIs and bulk biologics are clearly defined by statute (21 U.S.C. Sec 321(g)(1)(D)) and the CGMP regulations as components, this reviewer finds that commenter’s next remark, “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,” is, *at best*, an unnecessary statement that the guidance offered has clearly addressed to the extent that it should.

If the Agency agrees with the commenter about the need for guidance “regarding the applicability of the Quality System approach to manufacturers engaged in ‘Shared’ or ‘Divided’ manufacturing arrangements,” then that guidance should be provided in a separate document targeted to that issue and not in this guidance.

“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.”

This reviewer disagrees because: **a)** many suppliers are clearly “subject to 21 CFR Parts 210 and 211”; **b)**, *as the commenter pointed out in the preceding paragraph*, “the spirit of quality systems should be applicable to all stages of manufacture”; **c)** this document only offers guidance, and **d)** the use of the word “may” clearly indicate that the statement is an option that “may also be useful.”

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In addition, factually, suppliers of APIs, bulk biologicals, bulk drug products, and bulk finished pharmaceuticals are suppliers of **components** regulated by the FDA.

Based on the preceding facts, this reviewer again recommends that this commenter's misplaced remarks should be ignored.

**“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.”

While the commenter's rationale is specious, this reviewer has not problem supporting the change suggested provided the text remained fully compliant with all applicable CGMP **minimums**.

However, if the commenter's goal is, *as it should be*, to bring the terminology up to modern standards, then, a “life-long journey-based” approach that establishes that the process is valid should be adopted and changes should be addressed as integral parts of the maintenance of the qualification of the production processes and the batches of units produced by such production processes so that the process is provably valid.

Moreover, as this reviewer pointed out in the comments he submitted to this docket, in reality all of the “change” actions fall within the purview of the “Maintenance Qualification” (MQ) phase of the ongoing validation journey for each production process that begins in “Design/development Qualification” (DQ) and progresses to the MQ phase after the validity of fully function process has been established by a successful initial “Performance Qualification” (less commonly, but more aptly, “Evaluation Qualification” [EQ]) study of the process at the full-scale (or, minimally, near full-scale) production process.

Hopefully, the Agency will revisit this portion of the draft and considers this section from the more global view of an integral part of the MQ phase of the ongoing validation (see the FDA Compliance Policy Guide 7132c.08 “Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval,” updated 03-12-2004), as they should.

**“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.”

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Though this reviewer notes that the *minimum* expected of a regulated firm is compliance with all applicable statutes and binding regulations, *not just with 21 C.F.R. Part 211 as the commenter states*, this reviewer supports much of what the commenter states with the following important reservations:

- First of all, in any inspection in which a firm claims to be operating in conformance with any system, the FDA inspectorate has the responsibility and authority to inspect for compliance to that system.
- Second, the Agency will only need “to provide training to their pharmaceutical inspectorate as to how to conduct a review of the application of” quality management approaches “which are outside of current regulatory requirements” – not to “risk management approaches” because “risk management approaches” fall outside of the scope *per se* of quality-directed. Quality systems management which has, *among its “risk” goals*, the identification, avoidance and minimization of risk, and not, *per se*, the management of risk.

In this reviewer’s experience those firms claiming to be involved in “risk management” have CAPA programs that are in reality “CAPA” programs – because these firms are constantly operating in the “fire fighting” mode.

On the other hand, those firms that are truly quality oriented and use a “quality management” approach have “CAPA” programs – though these firms have effective corrective-action plans, their preventive-action plans are so strong that they rarely have to take any corrective action – however, most of these are, unfortunately, not in the drug industry.

Further, provided a regulated firm is truly operating in full compliance with the minimums of all applicable statutes and regulations, that firm should not expect to receive any “inspectional observations” *per se* for any optional system, *such as that offered in this guidance*, that that firm has not elected to adopt

**“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.

First of all, this reviewer does not agree with the commenter’s statement that the audit requirement stated “is difficult and onerous if not impossible to do well.”

Furthermore, unless a firm is able to audit its entire quality system on an ongoing basis so that, at least annually, all of its operational units have been audited, that firm does not truly have a valid quality system for that firm and it cannot validly assess the quality system that it claims to have implemented.

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This does not mean that once a year the firm should stop and audit everything – a full audit can be achieved by auditing defined portions of the firm's operational activities in, for example, the first 11 months of a year, restarting the 11-month audit cycle, and reserving the 12<sup>th</sup> month for a review of and report on the global quality system for that firm.

The rest of the commenter's soliloquy, "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" adds little of value.

Furthermore, this reviewer knows of none of today's pharmaceutical firm that come close to having comprehensive real-time universal monitoring systems, of the type alluded to by the commenter, that are validly self-auditing.

That is not to say that, *where such valid self-monitoring systems are in place*, the output of such systems cannot be incorporated into a firm's master audit plans.

Based on all of the preceding realities, this reviewer would recommend that the Agency retain the current text without modification.

**"Point #7: GMP (sic) references**

PDA notes there is an inconsistent level of detail when referencing specific GMP (sic) requirements. PDA recommends that the examples of specific GMP (sic) 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."

First, since this guidance does not reference any "specific GMP (sic) requirements," but only CGMP requirements and, historically, those who knowingly substitute an acronym "GMP" (sic) for the valid one used in this guidance, "**CGMP**," are subconsciously revealing their disdain for both compliance and true drug quality, this reviewer would suggest that the commenter's remarks should simply be ignored. [Note: In the 24 pages of guidance text, the acronym "CGMP" appears about 95 times (an average of about 4 times per page and the acronym "GMP" (sic) does not appear even once. Apparently, this commenter did not read, or if the commenter read this draft, they failed to notice the repeated use of the appropriate acronym "CGMP."]

Second, since the subject of this guidance is a "**Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**," the commenter should have recommended that "the examples of specific" **CGMP** "requirements and recommendations for maintaining quality be" appropriately increased in those areas where they are sparse, if the commenter were truly interested in improving the guidance and believed that the "inconsistent level of detail" was a problem.

However, this commenter did not do that.

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Third, If the commenter were truly interested in improving the guidance and believed that “examples of specific” **CGMP** “requirements” are needed to support each “particular point with regard to the implementation of a quality system approach,” then the commenter would have recommended adding more such examples.

Again, this commenter also did not do that.

Given the preceding, the commenter’s recommendations should be ignored.

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

<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
39	<p>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 other 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...</p> <p>First, this reviewer does not understand the point of the longwinded opening statements other than to introduce another PDA working group, the QU working group, who, at best, should viewed with suspicion by the Agency, since the PDA’s BU working group and their scientifically unsound pronouncements of Blend Uniformity can be taken as an indication of the soundness of the QU group. Second, the commenter was so “interested” in commenting here that it did not even notice that its comment had been truncated. Based on the commenter’s rationale, this reviewer can only infer that the comment was intended to recommend leaving out the first paragraph in the “<b>A. Background</b>” section addressed therein. Given the preceding realities, this commenter’s remarks here should be ignored.</p>	<p>While historical background information regarding the Pharmaceutical CGMPs for the 21<sup>st</sup> Century initiative is interesting, once 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 information.</p> <p>Those who do not learn from history are doomed to repeat its mistakes. Further, even the commenter admits that this is “useful historical information.” Finally, the information in the paragraph in question is validly a part of “<b>II. BACKGROUND AND PURPOSE A. Background</b>,” the topic under which the text appears. Factually, the text in question states, “In August 2002, the FDA announced the Pharmaceutical CGMPs for the 21<sup>st</sup> Century Initiative. In that announcement, the FDA explained the Agency’s intent to integrate <i>quality systems</i> and <i>risk management</i> approaches into existing programs with the goal of encouraging the adoption of modern and innovative manufacturing technologies. The CGMP initiative was spurred by the fact that since 1978, when the last major revision of the CGMP regulations was published, there have been many advances in manufacturing technologies and in our understanding of quality systems. Many pharmaceutical manufacturers are implementing comprehensive, modern quality systems and risk management approaches. The Agency also saw a need to address the harmonization of the CGMPs and other non-U.S. pharmaceutical regulatory systems as well as FDA’s own medical device quality systems regulations.” Since the preceding text is clear and, as even the commenter admits, “useful historical information,” this reviewer recommends that it should be retained in the guidance without alteration.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
44	<p>Replace manufacturing technologies with the phrase in italics: There have been many advances in “manufacturing technology and science” and in our understanding of quality.</p> <p>On the bases stated, this reviewer does not support the replacement proposed by this commenter. The text should remain unchanged here.</p>	<p>This statement would then be consistent with language from PQRI.</p> <p>Since the PQRI has previously repeatedly demonstrated its lack of understanding of sound science to this reviewer and failed to provide any rebuttal to this reviewer’s cogent observations that the BU working group’s comments on blend uniformity, though “science based,” were scientifically unsound, this reviewer and the Agency should discount it as a reliable source. Second, the commenter provides no substantive evidence to support the implicit claims that the commenter’s alternative presents. Third, the commenter reveals its fundamental lack of understanding of the English language when it speaks of “the phrase in italics” when the proposed change “manufacturing technology and science” is in quotes not italics. Fourth, as written, the phrase is ambiguous – does the commenter intend the meaning to be “in manufacturing technology and (manufacturing) science and in” or “in manufacturing technology and science, and in …” or?</p>
98, IIB:	<p>Please clarify how a firm can handle may handle different types of changes without the need for regulatory submission.</p> <p>Based on the realities stated, the Agency should ignore this request because it is not germane to the guidance issues being addressed.</p>	<p>Please refer to our cover letter Point # 2</p> <p>Because the referenced Point # 2 contains no rationale for its statements, this reviewer is at a loss to see how it can be used as a “rationale” here.</p> <p>Though the commenter’s request is interesting, it overlooks the reality that US statutes and binding FDA regulations establish the limits on the allowable “regulatory flexibility” – and not either the quality system or how it is implemented. Further, since there are FDA documents that directly address changes and the rules governing them, the commenter should address its requests and suggestions to those documents.</p>
113, II C	<p>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.</p> <p>This reviewer does not agree.</p>	<p>Please refer to our cover letter Point # 4</p> <p>First, the commenter’s Point # 4 does not address the text cited – factually, its Point # 3 does partly address this issue but even that point provides no rationale.</p> <p>Second, because there is no detailed CGMP Part for bulk drugs or active pharmaceutical ingredients that would apply to ‘Active Pharmaceutical Ingredients’ (APIs), the Agency appropriately limits this guidance’s scope to drug products.</p> <p>Third, because the next sentence, “It may also be useful to manufacturers of components used in the manufacture of these products,” clearly applies to APIs, the Agency already permits it to be applied to APIs because APIs are components!</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
148	<p>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.</p> <p>The commenter’s, at best, tangential and unfocused remarks here should be ignored.</p>	<p>In place of the adjectives (robust, modern, etc) describing the quality system, a philosophical discussion of the quality system is warranted.</p> <p>Guidance is supposed to guide not philosophize. In addition, the commenter’s remarks are unfocused and sloppy.</p> <p>For example, a “QS should apply throughout the entire” LIFE “of the product or service” (the use of the term “life cycle” confuses a systematic life-cycle-based approach to the generation and maintenance of a product or service with the actual reality that, for a given product [or service], LIFE is not cyclic but simplistically begins with its conception and proceeds until it ceases to be produced [or offered]).</p> <p>Second, fundamental to a “QS is an organization that ensures” AN “integrated approach to satisfy the particular safety and” THE QUALITY “needs of the specific” PROVIDER“, product” OR SERVICE, “and” ALL OF THAT ORGANIZATION’S CUSTOMERS.</p> <p>Third, a “quality system” cannot AFFIRM anything especially “interrelatedness” – factually the interrelatedness of any set of systems is defined by the inputs, operations, operators, controls and outcomes that make up the overall item or service provided.</p>
154, IIIA	<p>The definition of quality is inconsistent with the definition provided in the Glossary. “Achieving Quality” is much more than meeting product specifications. A better definition is required.</p> <p>Though the text in question does not attempt to define “quality,” but rather defines the phrase, “<i>achieving quality</i>,” this reviewer agrees with the commenter that a better definition is needed and proposes the following replacement for the draft’s Lines 154-157:</p> <p>“Every pharmaceutical product has established identity, strength, purity, and other quality characteristics designed to ensure the required levels of safety and effectiveness. For the purposes of this draft guidance document, the phrase <i>achieving quality</i> means achieving these characteristics for <u>all</u> the product units from the time the units are released until after the units have passed their expiration date.”</p>	<p>If “achieving quality” is defined as it is written 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.</p> <p><i>Since, in general, the quality expectations for drugs are higher than those for most other goods, it is important that each of the units in each batch or lot of product be ensured of meeting its established identity, strength, purity, and other quality characteristics to ensure that the unit or units administered to each patient should meet each and every one of these quality criteria at release and, provided they have been properly handled after release, are assured of being both safe and effective from release until after their expiration date.</i></p> <p>This is especially critical when the patient only receives one or a few (&lt; 10 units) in a given treatment regimen.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
171	<p>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”.</p> <p>This reviewer cannot agree with the commenter. Obviously, using risk assessment “in determining the need ... for changes to existing processes” is one aspect of the use of corrective action in determining the need for “corrective action.” Therefore, the commenter’s suggestion here is duplicative to say the least.</p>	<p>As written, risk management is part of setting specifications 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. Risk mitigation methods are based on process/product knowledge as well as priority.</p> <p>This reviewer is at a loss on where to begin to address a rationale that addresses “risk management” and “risk mitigation” but does not specifically directly address the topic under discussion, “Risk assessment.”</p> <p>“As written, risk management is” NOT even addressed in Line 171.</p> <p>Moreover, all that the draft says about risk management is, “Risk management can guide the setting of specifications and process parameters.” Yet, this commenter twists what is said into “risk management is part of setting specifications and process parameters <b>as well as determining the need for discrepancy investigation and corrective action.</b>”</p>
185, III E	<p>Change “Change Control” to “Change Management”.</p> <p>This reviewer has no problem with the commenter’s remarks and could support the use of the more-general term, “Change Management,” over “Change Control” provided the text remained fully compliant with all applicable CGMP minimums. However, as this reviewer pointed out in the comments he submitted to this docket, in reality all of the actions fall within the purview of the “Maintenance Qualification” (MQ) phase of the ongoing validation journey for each production process that begins in “Design/development Qualification” (DQ) and progresses to the MQ phase after the validity of fully function process has been established by a successful initial “Evaluation Qualification” (EQ) study.</p> <p>Hopefully, those reviewing this commenter’s remarks and those of this reviewer will revisit this portion of the draft and generalize it into guidance that considers this section from the more global view of “Maintenance Qualification” as they should.</p>	<p>Please refer to our cover letter Point # 5.</p> <p>First, the commenter’s “cover letter Point # 5” reference is incorrect – the correct reference is to “Point # 4.”</p> <p>Second, the commenter’s stated rationale (in its cover letter’s <b>Point # 4</b>) is specious.</p> <p>Yet, this reviewer has no problem supporting the change suggested <u>provided</u> the text remains fully compliant with the applicable CGMP <b>minimums</b>. However, if the commenter’s goal is, <i>as it should be</i>, to bring the terminology up to modern standards, then, a “life-long journey-based” approach, which <i>continually</i> establishes that the process is valid, should have been proposed, and changes should have been addressed as integral parts of the maintenance of the qualification of:</p> <ul style="list-style-type: none"> <li>a. the production processes and</li> <li>b. the batches or lots of units produced by such production processes</li> </ul> <p>so that the process and the drug product produced are both provably valid.</p> <p>However, the commenter failed to suggest either of the courses of action suggested – indicating no such improvement interest on its part.</p>

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Gd Line # & Sec.	Comment & Reviewer’s Remarks	Rationale & Reviewer’s Basis
195	<p>Change “towards continuous improvement” to “towards innovation and improvement”</p> <p>This reviewer objects to the commenter’s suggestion because it is: <b>a)</b> ignores the draft’s stated intent for the topic of the sentence, “<i>change</i>,” and <b>b)</b> the commenter’s rationale addresses a tenet “of the FDA’s initiative,” that does not directly speak to the control of “<i>change</i>” in a given manufacturing process as it should.</p>	<p>One of the basics tenets of the FDA’s initiative is to enable innovation in the manufacturing science of pharmaceuticals.</p> <p>The current text, “In this guidance, <i>change</i> is discussed in terms of creating a regulatory environment that encourages change towards continuous improvement,” accurately reflects a quality approach to change that only permits change when it improves some aspect of the drug product or the process that produces that drug product.</p> <p>The commenter’s alternative, “towards innovation and improvement” would permit a “<i>change</i>” that does not improve the product or the process from the point of view of quality (e.g., an “innovation” that greatly reduces cost but also reduces quality within the limits “allowed” in the firm’s filing – an anti-quality action to say the least).</p> <p>The commenter’s rationale phrase, “to enable innovation in the manufacturing science of pharmaceuticals” speaks to innovation in “manufacturing science,” a topic that is peripheral to innovation in a given manufacturing process, the object of the “<i>change</i>” being discussed here.</p> <p>Thus, the draft’s text should be preserved because it properly restricts changes to those that are an improvement that does not reduce quality while the commenter’s proposed alternative does NOT.</p>
204	<p>Replace Section F “The Quality Unit: as written with the recommended section located in Appendix “b”.</p> <p>This reviewer does not support the commenter’s suggestion here (<b>see</b> the reviewer’s remarks on “Appendix ‘B’”).</p>	<p>PDA believes the language in the supplied rewritten section is clearer and consistent with current expectations and practices.</p> <p>This reviewer finds that the commenter’s alternative is clearly NOT consistent with “current expectations and practices” (<b>see</b> the reviewer’s remarks on “Appendix ‘B’”)</p>
241	<p>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.</p> <p>This reviewer sees no need for the current document to compare “relationship between the systems” listed in CPGM 7356 and the Quality Systems Model.</p>	<p>This will assure there is no conflict between the two documents and/or the two approaches.</p> <p>Apparently, this commenter does not realize that the 4-part Quality Systems Model presented fully applies to each of the systems discussed in CPGM 7356.</p> <p>Thus, if any additional verbiage is needed, all that the Agency need do is add a statement that reflects the preceding reality.</p>
290, IV	<p>If FDA regulatory and routine GMP (sic) inspection coverage will remain focused on the specific CGMP regulations, how will inspections incorporate the application of risk management which may be outside of the regulatory requirements?</p> <p>The Agency should ignore this commenter’s, at best, misguided request.</p>	<p>Please refer to our cover letter Point #6.</p> <p>Again, the correct reference is “Pont # 5.”</p> <p>The concept, “risk management,” is outside the scope of both: <b>a)</b> the model addressed in this guidance and <b>b)</b> the limits established by the CGMP <i>minimums</i>.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
304, IV A	<p>There is a concept underlying in this section of senior management responsibility and corporate knowledge and initiatives to address compliance issues. As a part of inspections, FDA can use this concept to evaluate a non-compliant situation in concert with risk management (risk mitigation) tools.</p> <p>The commenter’s ambiguous and convoluted remarks should simply be ignored.</p>	<p>Please refer to our cover letter Point # 5.</p> <p>This reviewer notes that the commenter referenced the correct point in its cover letter this time.</p> <p>The commenter’s first statement is unintelligible. Though the commenter’s second statement is at least clearer, it establishes a linkage between “a non-compliant situation” and “risk management (risk mitigation) tools” that does not exist under CGMP and speaks of the first sentence as “this concept” even though the commenter’s statement does not state any recognizable concept.</p>
306	<p>Please define Management and Senior Management.</p> <p>This reviewer does not agree with the commenter here.</p>	<p>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.</p> <p>First of all, the term “management,” though it is has more than one definition, is well and properly defined in most dictionaries and should not, therefore, be defined in this guidance just as words with common definitions, such as “different” and “provide,” need not be defined.</p> <p>Second, the phrase “top management” should remain indeterminate to allow each regulated firm to decide exactly where, in their management hierarchy, the firm should draw the line between top management and any lower level.</p> <p>Third, the commenter’s use of the word “interpret” when the appropriate word here should have been “understand,” belies their feigned concern for the need for the definitions requested.</p>
367	<p>“It is recommended under a modern quality systems approach that a formal process be established to submit change requests to directives”.</p> <p>Though this reviewer sees no need for clarification here, this reviewer leaves it up to the Agency here. If any change is needed, this reviewer suggests simply changing the word “directives” to the phrase “the firm’s directives that fall within the operations covered by the firm’s quality system.”</p>	<p>PDA is unclear as to which directives FDA is referring to. Please clarify.</p> <p>Those who understand quality systems know that “directives” refers to any approved written statement that directs the activities of a firm, including, but not limited to, the firm’s “mission, vision and values statements, policies, standard operating procedures, and work instructions.”</p>
395	<p>change “identify resources” to “allocate resources”.</p> <p>This reviewer cannot support this commenter’s obviously misplaced suggestion.</p>	<p>In order to have an effective quality system, resources must be allocated not just identified.</p> <p>Since this sentence states, “Under a quality system, managers would be expected to use quality planning to identify resources and define methods to achieve the quality objectives,” the sentence properly states the <b>planning</b> process’ goals. Unless, in planning, the resources required are identified, <i>when the plan is later implemented</i>, the required resources cannot be assured of being available for allocation.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
405	<p>Add process to “an assessment of the product and process”.</p> <p>This reviewer agrees that the sentence containing the cited text should be changed and suggests: “Such a review typically includes an assessment of the incoming and in-process materials used to produce the finished product, the product produced, and the process used as well as customer needs (in this section, <i>customer</i> is defined as the recipient of the product and the product is the goods or services being provided).”</p>	<p>This acknowledges that quality systems should address the process not just the product meeting specifications.</p> <p>This reviewer agrees with the commenter’s rationale here but sees that more is required than the simple change proposed by the commenter.</p>
428, IVA5	<p>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.</p> <p>This commenter does not agree because these records bear on compliance with the applicable CGMP regulations as well as with the firm’s quality system.</p>	<p>Routinely making these types of internal records available to FDA investigators during inspections will compromise their value to the firm.</p> <p>First, in truly robust quality systems, these records are not internal records; they are records that are open to all customers, including the FDA personnel who inspect the firm.</p> <p>Since the adoption of a quality systems approach is optional, <i>as is any such guidance</i>, firms that truly believe that the FDA’s inspecting these records “will compromise their value to the firm,” then those firms should decline to follow this guidance.</p>
613, IVC3	<p>Please include phrase in italics: The quality system 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”.</p> <p>Neither this reviewer nor the applicable CGMP regulations nor the approaches promulgated by the recognized quality system standards support this revision.</p>	<p>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.</p> <p>The word “periodically” permits the flexibility needed by the firm and the language in the draft permits third-party audits.</p> <p>However, true compliance with the applicable CGMP regulations (in 21 C.F.R. Sec. 211.84) and the expectations of quality systems expect such audits.</p> <p>Moreover, a firm cannot build quality into their product or processes if they do not demonstrably control the quality of the inputs supplied by the firm’s outside contractors.</p>
622	<p>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 approval market applications”.</p> <p>This reviewer does not support the commenter’s suggestion.</p>	<p>If the document is meant to be applicable to development activities as well, this will allow for flexibility for implementing QS during development.</p> <p>This commenter seems not to understand that, <i>under a quality system</i>, there must be “procedures to verify that materials are from approved suppliers.”</p> <p>If the firm does not want to adhere to what a quality system requires, then, that firm should elect to not pursue the quality system option offered by this guidance.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
630	<p>Change “quality control unit” to quality unit.</p> <p>This change should not be made.</p>	<p>This becomes consistent with the distinction between Quality Unit, QC and QA described in Section II F.</p> <p>The commenter apparently failed to read the guidance’s footnote 7, which states, “Generally, the term <i>quality unit</i> is used in this guidance. However, <i>quality control unit</i> is used when directly quoting parts 210 and 211.”</p> <p>The passage in question is obviously “quoting” (paraphrasing directly from 21 C.F.R. Part 211, “(certain changes require review and approval by the quality control unit (see § 211.100(a))” as the reference “(see § 211.100(a))” clearly indicates.</p>
646	<p>Change from “process weakness” to areas of “higher risk”.</p> <p>This reviewer suggests that the commenter’s suggested change here should be ignored. In addition, the reviewer finds that this suggestion seems to be baseless.</p>	<p>The concept of higher risk is consistent with this document.</p> <p>First, this reviewer finds that the phrase quoted has been artfully taken out of context. Second, though the “concept of higher risk is consistent with this document,” the topic that is being discussed is the process. Since this is the case, the term “process weakness” is much more appropriate than “higher risk.” Moreover, <i>though usable</i>, the applicable “risk” term, “process risk,” is NOT appropriate because an area of process weakness may carry with it little or NO risk. [For example, a crystallization step that requires several days to complete is a “process weakness” but not, <i>per se</i>, a “process risk.”]</p> <p>This change should be ignored because the topic being discussed in this narrative section is areas of the “process” and not areas of “risk.”</p>
730	<p>Delete word “statistically” from “invalidation of test results should be scientifically and statistically sound and justified.</p> <p>This reviewer with the commenter agrees that the word “statistically” should be deleted along with the word “and” that follows it. However, this reviewer finds that other changes are also needed and suggests that the sentence containing this text be changed to read:</p> <p>“Invalidation of test results should be: <b>a)</b> scientifically sound, <b>b)</b> based on an analyst error, method weakness, or equipment failure established from the critical evaluation (investigation) of all data, and <b>c)</b> justified.</p>	<p>This is the first time FDA has required 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.</p> <p>The commenter’s rationale proverbially “strains at the gnat and swallows the camel.”</p> <p>The changes suggested by this reviewer reflect the reality that, <i>in a robust CGMP-compliant quality system</i>, conclusive proof of a cause must be found before test results can be unequivocally “invalidated.”</p> <p>Factually, since the term scientifically sound encompasses all proper uses of statistics, the phrase, “scientifically and statistically sound,” is an illogical and grammatically incorrect construction.</p>
770, IVC5	<p>Delete the phrase “be handled as discrepancies and”.</p> <p>This reviewer knows that this comment should be ignored.</p>	<p>Customer complaints should not automatically be considered discrepancies.</p> <p>Under a quality system, all customer complaints bear on customer quality and should be treated as discrepancies and, under CGMP, investigated because they plainly bear on a quality issue.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
808	<p>Delete the requirement the “need to audit the entire system at least annually”.</p> <p>This reviewer recommends that the Agency should ignore this commenter’s less than appropriate suggestion.</p>	<p>Please refer to our cover letter Point 6.</p> <p>Unless a firm is able to audit its entire quality system on an ongoing basis so that, at least annually, all of its operational units have been audited, that firm not only does not truly have a valid quality system but also cannot validly assess the overall “quality system” that the firm claims to have implemented.</p> <p>However, this does not mean that once a year the firm should stop and audit everything – a full audit can be achieved by auditing defined portions of the firms operational activities in, for example, the first 11 months of a year and reserving the last month for a review of and report on the global quality system for that firm</p>
823, IV D	<p>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.”</p> <p>This reviewer does not support the commenter’s request here and recommends that it be ignored.</p>	<p>Addition of risk to patients is consistent with the concepts in the FDA GMPs (sic) for the 21<sup>st</sup> Century initiative.</p> <p>First of all, since “risk to patients” is a quality issue, there in absolutely no need to add it as the commenter requests.</p> <p>Second, as far as this reviewer knows, “GMPs” is not an Agency-recognized acronym – the pertinent proper FDA-recognized acronyms are “CGMP,” the proper acronym for the 4-word phrase, “current good manufacturing practice,” and “GMP’s,” the narrowly applicable (<b>see</b> 21 C.F.R. Sec. 26.3) acronym for the phrase, “Good Manufacturing Practices,” which is defined in 21 C.F.R. Sec. 26.1(c).</p>
889, V	<p>Change “quality professionals” to “pharmaceutical manufacturers”.</p> <p>The commenter’s unsupported change should be ignored.</p> <p>Moreover, the guidance statement, “Quality professionals are aware that good intentions alone will not ensure good products,” to which this commenter is referring here should simply be deleted.</p>	<p>All pharmaceutical operations personnel must be responsible for the quality of the products and processes.</p> <p>First, the commenter’s rationale is flawed and does not support the change suggested <b>because</b>, IF all “pharmaceutical operations personnel must be responsible for the quality of the products and processes” THEN all such personnel must, similarly, be quality professionals.</p> <p>Second, the statement in question, <i>though true</i>, is not germane to the subject of this guidance, <b>“Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations.”</b></p> <p>Moreover, this statement adds nothing of value to the guidance, in general, or to the <b>“Conclusion”</b> section, in specific.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
1022, Glossary	<p>Recommend changing the definition to “a person of organization (internal or external) that receives the output of a process anywhere along the product’s life cycle.”</p> <p>This reviewer does not support the commenter’s recommendation.</p> <p>However, this reviewer does suggest slightly changing the guidance text so that it reads:  <b>“Customer</b> – a person or organization (internal or external) that receives a product or service anywhere <del>along</del> in the life of a service or a product’s <del>life cycle</del>.</p>	<p>Clarification; recognizes that all processes have inputs and outputs.</p> <p>The commenter’s clarification misses the point; customers receive tangible things – products (including incoming materials, containers, closures, labeling, packaging materials, in-process materials, finished drug units, finished packaged product, samples, etc.) or services (e.g., shipping papers, reports of analysis, release documents, notification of discrepancies, acceptance/rejection notices).</p> <p>Since these include items that are inputs to specific process steps, the language used is more appropriate.</p> <p>The reviewer’s changes address the fact that services have customers and that customers receive what they do at some point in the life of the service or product – only after the life of the product or service provided finally expires are there no customers for that product or service.</p>
1029, Glossary	<p>Delete the second sentence.</p> <p>The commenter’s suggestion should be dismissed with prejudice.</p>	<p>It is not clear that metrics can be qualitative.</p> <p>The commenter’s rationale statement is incorrect and displays the commenter’s ignorance of the principles of quality as they apply to attribute assessment (<b>see</b>, for example, ANSI/ASQC S2-1995, “<b>Introduction to Attribute Sampling</b>,” and ANSI/ASQ(C) Z1.4-1998 (-1993), “<b>Sampling Procedures and Tables for Inspection by Attributes</b>”).</p> <p>All attribute assessment procedures are qualitative metrics (for example, visually examining representative samples of a batch of “white” tablets for their defect levels and making decisions based on the findings from the evaluation as to whether or not the batch inspected is acceptable for release.</p>
1047, Glossary	<p>As previously mentioned this definition is inconsistent with the one provided in the body of the Guidance at Lines 154-157.</p> <p>The commenter’s suggestion here is simply wrong. However, upon reflection, this reviewer suggests that the definition of “<b>Quality</b>” be changed to read:  <b>“Quality</b> – a measure of a product’s or service’s conformance to or divergence from the customer’s stated or implied minimum needs.”</p>	<p>This seems a better definition than “meeting specifications”:</p> <p>The commenter has confused the definition of “<i>achieving quality</i>” in Line 154-157 with the definition of “<b>Quality</b>” given in Lines 1047-1048.</p> <p>The draft guidance’s definition confuses ability (capability), which is a process reality, with the customer’s needs (stated or implied), which are measures of how that which is delivered (the product or service) conforms to or diverges from the customer’s needs.</p> <p>The reviewer’s alternative removes this confusion.</p>

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<b>Gd Line # &amp; Sec.</b>	<b>Comment &amp; Reviewer’s Remarks</b>	<b>Rationale &amp; Reviewer’s Basis</b>
1053, Glossary	<p>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”.</p> <p>The commenter’s suggestion should be ignored. However, this reviewer does recommend redefining “Quality Control” as follows:  <b>“Quality Control — <del>the steps taken during the generation of a product or service to ensure that it meets requirements and that the product or service is reproducible</del> a system of verifying and maintaining a desired level of quality in a product, service or process by careful planning, use of proper equipment, continued inspection, and corrective action when required, and the organizational unit with the primary responsibility for overseeing such activities”</b></p>	<p>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.</p> <p>The commenter forgets that, by CGMP regulation, quality control is also charged with sampling and monitoring activities in addition to reviewing, not actually performing, all evaluations (tests and examinations). Moreover, the commenter’s suggestion shows a less than sufficient understanding of the fact that a “lab” tests or measures variables, examines attributes and, overall, a “laboratory” evaluates characteristics.</p> <p>The reviewer’s alternative changes the definition to match the <b>dictionary definition of quality control</b> because that definition fits the CGMP view of the term much better than the definition provided in the draft.</p>
1071, Glossary	<p>Change the definition of Quality System 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 goods and services.</p> <p>This reviewer does not support the commenter’s recommendation, but does suggest making minor revisions:  <b>“Quality System — formalized business practices that define management responsibilities for organizational structure, processes, procedures and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement. In a CGMP regulatory context, the quality system establishes the foundation that supports the effective functioning of the operational units that fall within the CGMP-compliant Quality System adopted.”</b></p>	<p>To provide the reader with an understanding of the broad scope and philosophy of the quality system.</p> <p>The current definition not only already provides the reader with a general “understanding of the broad scope and philosophy of the quality system” but also provides a definition that matches the detailed <b>“Quality System Model”</b> presented in this guidance.</p> <p>The commenter apparently does not understand that a <b>“Quality System”</b> is the overarching system generated by management that defines the “management responsibilities for organizational structure, processes, procedures and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement.”</p> <p>Apparently, the commenter either did not carefully read this guidance or does not understand, as a fundamental level, what a “Quality System” is.</p>

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Review of “**Appendix B**”

This commenter proposes the following alternative text for this section in the draft guidance (for clarity, the commenter’s changes are bolded):

“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 #I, comment 91.”

While this reviewer finds the commenter’s changes, he finds that, for the most part they should be rejected and proposes the following alternative text for “**The Quality Unit**” section:

“Many of the modern 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~~ among the quality control (QC), ~~and~~ quality assurance (QA) *and regulatory affairs (RA)* functions.

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- QC usually consists of assessing the suitability ~~testing~~ of incoming components, containers, closures and labeling, ~~selected~~ critical in-process materials and the finished products to:
  - a. Evaluate the performance of the manufacturing process, ~~and~~
  - b. Ensure adherence to proper specifications and limits, and
  - c. Determine the acceptability of each batch or lot for release.
- QA primarily includes the review and approval of all procedures related to production, maintenance, and review of associated records, and auditing, and performing trend analyses. In some firms, QA also determines the acceptability of each batch or lot for release.
- RA typically acts as the quality function's bi-directional interface between the other quality functions and the FDA."

This commenter suggests the preceding changes to address the reality that while quality control is supposed to have "(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit" (21 CFR Sec. 211.22(b)), quality control must "have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, ... The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company" (21 CFR Sec.211.22(a)).

This distinction is increasingly important as more and more manufacturers *outsource* their sample evaluation programs to contract laboratories leading to the reality that increasingly such manufacturer's on-site laboratories that report to the QC function do less and less testing.

In addition, this commenter understands that, *given the realities that exist in the structuring of most pharmaceutical companies*, this guidance should recognize the important agency/manufacturer interface role of regulatory affairs (RA) units as a part of the quality control unit.

This is the case because RA typically oversees the conduct of agency inspections, files all submission documents and annual reports, and addresses all issues that arise with the agency.

"This guidance uses the term *quality unit*<sup>7</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 modern quality systems ~~is ensuring~~ that ensure that the various operations associated with all systems are appropriately approved, implemented, conducted, ~~and~~ monitored, and controlled. The CGMP regulations specifically assign the quality unit the authority to review and approve the quality system (as defined by the 'any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications,

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<sup>7</sup> Generally, the term *quality unit* is used in this guidance. However, *quality control unit* is used when directly quoting parts 210 and 211.

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standards, sampling plans, test procedures, or other laboratory control mechanisms’ [21 CFR § 211.160(a)] used by the firm). 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>8</sup>”

The additions suggested by this reviewer are provided to ensure that the fundamental *scientifically sound* and *appropriate* requirements of the CGMP regulations for finished pharmaceuticals are explicitly stated.

The other changes suggested by this commenter are intended to recognize that approval, implementation, and modification of a CGMP-compliant quality system, as defined in 21 C.F.R. Sec. 211.160(a)), fall under the authority of the quality unit.

“Other CGMP assigned responsibilities of the quality unit are consistent with a modern quality system approaches (see § 211.22) and include, but are not limited to:

- *Ensuring the controls are scientifically sound and appropriate as well as ensuring that the samples sampled and the samples evaluated are representative of the population (batch or lot) from which they are taken.*
- 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
- Approving or rejecting incoming and in-process materials, and drug products — although such activities do not substitute for, or preclude, the daily responsibility of manufacturing personnel to build quality into the product
- Reviewing production records and overseeing the investigation~~s~~ of any unexplained discrepancies

Under a robust quality system, the product and process development units, manufacturing units, and the quality unit can remain independent, but still be included in the total concept of producing quality products. In very small operations, a single individual can function as the quality unit. That person is still accountable for implementing all the controls and reviewing results of manufacture to ensure that product quality standards have been met.”

The first inserted bullet, “Ensuring the controls are *scientifically sound* and *appropriate* as well as ensuring that the *samples* sampled and the *samples* evaluated are *representative* of the *population* (batch or lot) from which they are taken,” was added to ensure that the reader recognize that the “scientifically sound” and “appropriate” are the foundation of any modern quality system for a CGMP-compliant pharmaceutical process (21 CFR Sec. 211.160).

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<sup>8</sup> See Reference #1, comment 91.

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In addition, this bullet sets forth the need for **all samples** to be *population representative* because the goal of a CGMP-compliant quality system must be to ensure that the **untested units** probably meet all of their specifications.

A corollary to the preceding is that, unless a *scientifically sound and appropriate representative sample* is evaluated, the results from any sample evaluation **cannot** validly be used to do what is required, *namely, predict with a high degree of confidence that the unevaluated units meet all of their specifications.*

The suggested change in the bullet that begins “Approving or rejecting ...” should be made because, *if you are going to build quality in*, you **must** start doing so during development.

Moreover, a manufacturer **cannot** build in quality if that manufacturer does **not** address and appropriately control the quality of all of the incoming materials used in the process!

The suggested change in the last bullet recognizes that the quality unit should appropriately oversee the conduct of any production discrepancy investigations because the production unit that generated the discrepancy is usually better equipped to conduct the investigation than the quality unit *per se*. [Note: In this context, the laboratories reporting to the quality unit are a production unit – **they produce evaluated results that the quality unit reviews and uses in discharging its decision making responsibilities with respect to the materials or products evaluated.**]

The need to explicitly include the “*product and process development units*” in the list of units outlined in a “robust quality system” stems from the reality that building quality into a product must begin with those who interactively develop both the product and the process for its manufacture.

Hopefully, both this commenter will carefully read and accept these rationale-supported changes to this section of the draft.

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**C-07 Comments By PhRMA, Posted 7 December 2004**

PhRMA begins by stating:

“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 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.”

This reviewer is bemused by the commenter's remarks here because they are oblivious to the reality that the true reason for no need for the submissions cited will be that those changes will have been defined and submitted to the Agency as an integral part of the outcomes of the studies that truly build quality into a given process before the process is submitted and not, as the present reality, after uncontrolled or unexpected events require such changes to be developed and validated in response to said events.

Simply, a firm that truly builds in quality under a quality system that starts in the product and process design stage and progresses as the process and product mature to being both adequately controlled and truly well-defined and robust at the full-scale level should have no need to change that process' or product's controls after Agency approval is obtained by the drug product sponsor except in rare instances.

However, because a true systematic building-in of quality is so rare in today's pharmaceutical, the commenter incorrectly believes that the quality systems approach *per se* will reduce the need for submissions rather than the systematic building-in of predictable quality based on the appropriate use of statistical quality

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control to establish the ongoing validity of both the process and the product it produces.

This having been stated, let us review this commenter's statements.

PhRMA's reviewed comments are as follows:

“General Concerns/Recommendations

PhRMA agrees with the desire to harmonize CGMPs globally wherever possible. With the ongoing work to develop ICH Q9 Risk Management, ICH Q10 on quality systems, and possibly ICH Q11 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.”

While this reviewer understands the commenter's position, this reviewer would caution both the commenter and the Agency to make certain that the guidance adopted conforms to the clear requirements of the applicable CGMP regulations as well as the recognized concepts clearly set forth in the applicable quality systems including the one most applicable to those who manufacture, process, pack, or hold finished pharmaceuticals, namely the applicable “ISO 9000” series of standards and the ISO-9000-derived standard, “ISO 17025.”

All that should be harmonized in this guidance are the quality systems approaches used.

This “harmonization” should be done in a manner that harmonizes the quality systems approaches used with CGMP and nothing else – because that is what the law requires.

“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.”

Since this commenter provides no suggestions as to “the process for achieving this should be further defined” and the guidance seems to be comprehensive enough, this reviewer suggests that this request be deferred until the commenter provides substantive information in support of its request.

“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

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sections from 21 CFR 210/211 may mislead readers into believing that the content of this guideline reflects the Agency’s current interpretation of the GMP (sic) regulations. We suggest removing these partial quotations from the document and instead providing citations to the regulations.”

First this reviewer notes that the commenter knowingly misidentifies the CGMP regulations as the “GMP (sic) regulations” indicating that this commenter is continuing its apparent ongoing efforts to misrepresent 21 C.F.R. Parts 210 and 211 and, worse, ignore the statutory import of 21 U.S.C. Section 351(a)(2)(B).

This reviewer does not support the commenter’s suggestion because he has found that many in the industry do not know, *much less understand*, the CGMP regulations and finds that “these partial quotations” give the reader with necessary information and valuable insights that excluding the “quotations” would fail to provide.

“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 21 CFR 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.”

This reviewer disagrees, since the word “expected” is properly used and restricted to required elements of any valid quality system, the text should not be so modified.

When discussing what is *expected* in the Quality System Model presented, the Agency is only stating a factual reality.

Furthermore, the guidance rightly specifies what is *expected* of those in the industry who elect to implement a Quality Systems approach while: **a)** clearly stating that adopting such is an *optional* approach that the industry *may* use **and b)** outlining a CGMP-compliant “Quality Systems Model” to assist those who wish to use this approach.

Therefore, the Agency should leave the expression of the guidance as it is currently and reject the commenter’s less than helpful comments here.

“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.”

Factually, the commenter is wrong — neither risk management nor risk assessment are key to the Agency’s approach — they are only tools to be used in the manner described in this guidance.

Factually, “Risk Assessment” is the only aspect of the “**Evaluation Activities**” facet of “**THE QUALITY SYSTEMS MODEL**” presented that addresses “risk.”

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Factually, risk elimination is the hallmark of a truly robust quality system — one that approaches risk as something to be assessed and eliminated.

In this reviewer’s experience, quality systems that focus on “risk” from the viewpoint of risk management/risk assessment tend to be less robust than those who approach “risk” from the viewpoint of risk assessment/risk minimization.

Thus, this reviewer would suggest that the Agency should not expand “risk assessment section of” the quality systems model presented.

If anything, this reviewer would recommend that the Agency revise that Evaluation Activities facet of the “Quality Systems Model” presented to discuss the topic as one of *risk assessment* and *risk minimization* rather than just *risk assessment* as it now does.

Failing to take this option, this reviewer recommends that, with some small changes, the guidance should remain as it is when it comes to “risk management/risk assessment.”

**Review of commenter’s “Specific Comments by Section and Line Reference”**

**“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.”

This reviewer disagrees with the commenter because it is obvious that this commenter’s objection and justification thereof are based on a misreading of what the statement in question, “This guidance describes a comprehensive quality systems model, which, if **properly** implemented, will allow manufacturers to operate robust, modern quality systems that are fully compliant with CGMP regulations.”

All that the statement says is that the guidance describes a “... quality system model, which, if implemented, will allow firms to operate ... quality systems that are fully compliant with CGMP regulations” not, as the commenter implies “fully compliant” with any and all of the other applicable “requirements, and regulations that manufacturers must follow.”

Since the text is clearly limited to “fully compliant with CGMP regulations” and seems to be factually supported by this reviewer’s reading of the guidance provided, this reviewer suggests that the Agency simply ignore this apparently misguided comment and only make the small change (noted in red) proposed by this reviewer.

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

Since the commenter fails to specify what are the requirements to which it is speaking, neither this reviewer nor the Agency should attempt to interpret what the commenter meant to convey.

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Since the commenter “agrees with this section,” this reviewer sees no need for any further comment here.

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

This reviewer does not agree with the commenter’s suggested change because, rather than clarifying “the scope to the reader,” the proposed change unnecessarily limits that scope.

If the Agency wishes to explicitly include “API’s,” then this reviewer suggests that the sentence in question be revised to read, “It may also be useful to manufacturers of active pharmaceutical ingredients and other components used in the manufacture of these products.”

However, this reviewer sees no compelling need to make the revision suggested.

**“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.”

This reviewer does not agree with the commenter’s suggestion here because the section in question covers both *risk management* and *risk assessment*.

Since this commenter did not suggest changing the text to delete the mention of *risk assessment*, this reviewer must recommend that the title alteration proposed should be ignored.

Furthermore, contrary to the commenter’s statement, *risk assessment* is a precursor to *risk management* and not necessarily “part of risk management.”

For example, in truly robust quality-seeking quality systems, the operative “risk” terms are *risk identification*, *risk assessment* and *risk elimination*, and the overall approach is *risk minimization*.

Moreover, firms led by their management to continually improve quality usually treat “risk management” as anti-quality.

This is the case because “risk management” unnecessarily accepts the premise that quality risks need only be managed rather than eliminated.

Since the pursuit of “product quality” is supposed to be more important in the pharmaceutical industry than it is in most other industries, the Agency and the ICH should see the wisdom changing the root concept from the complacent “risk management,” to the pro-active, “risk minimization.”

Further, this reviewer would recommend changing the text in Lines 169 to 173 to read:

“The concept *risk management* is a major focus of the ‘Pharmaceutical CGMPs for the 21<sup>st</sup> Century Initiative.’ Risk management can guide the setting of specifications and process parameters. Risk assessment is also used in determining the need for discrepancy

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investigations and corrective action. ~~As~~ When risk assessment<sup>5</sup> is used more formally by manufacturers, it ~~can~~ should be implemented within ~~the~~ a quality system framework. It should be noted that the CGMP regulations for finished pharmaceuticals (21 CFR Part 211) establish risk-based minimums for components, process, in-process materials, and drug-product quality assessment for acceptability for release that, given their timeframe and wording, set a minimum level of confidence that is **not less than 95%** – a level of confidence that is below today’s recognized ‘de facto’ standards for quality excellence (‘Six Sigma’).”

[**Note:** The wording changes suggested are designed to guide the reader to an understanding that, *when used*, risk assessment should be incorporated into the foundation of the quality system framework used. The reviewer’s added statement is provided to ensure that all parties clearly understand that the CGMP regulations for finished pharmaceuticals clearly establish risk-based quality *minimums* for each batch of drug product that, *based on their timeframe and wording*, set a 95%-confidence-level floor (*minimum*) (with established and justified “acceptable quality levels” for predicted out-of-specification units (percent non-conforming) between 0.1 % [1 in a 1000] and 1+ % [1 or more in a 100]) for each “batch” quality characteristic that a given drug product is required to meet before each batch can be accepted for release (as *per* 21 C.F.R. Sec. 211.165(d)). In addition, that added statement properly places the CGMP regulations’ quality *minimums* below today’s current “de facto” “Six Sigma” quality expectations.]

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

As this reviewer’s previous comments on the subject of “risk” clearly establish, this reviewer objects to this commenter’s request here.

In this commenter’s view, the current draft has spent more than enough words about this topic.

“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.”

Though this reviewer does not think that “a guidance document” is needed “to provide direction and prevent compliance issues,” he does agree with the commenter that the paragraph in Lines 193 to 198 should be revised to provide a clearer understanding (“more definition”) of this statement.

In that regard, this reviewer suggests that paragraph be revised to read:

“A quality system also contains change control activities, including quality planning and control of revisions to specifications, process parameters, and procedures. In this guidance, *change* is discussed in terms of creating a regulatory environment that encourages change towards continuous improvement in the quality of the process, without adversely affecting in-process quality, or the quality of the product. This means a manufacturer is empowered to make changes ~~based on~~ that reduce the variability of materials used in manufacturing and otherwise optimization ~~of~~ the process ~~from learning over time~~ based on the ongoing use of statistical control techniques that permit the manufacture to separate the effect of critical characteristic variation from random outcome fluctuation. Such quality

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<sup>5</sup> This concept is being developed under the ICH Q9 Risk Analysis Expert Working Group.

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improvement activities can be pursued without the need for a regulatory filing whenever the regulated firm has explicitly incorporated such programs into their approved submissions. Under such circumstances, all that the firm need do is report its progress on improving the quality of its drug products in the firm's annual report (AR)."

[**Note:** In the first instance, the added phrase "in the quality of ..." is added to point out that the goal of CGMP-compliant improvement should be to improve the quality of the process without adversely affecting product quality or, better, to improve the quality of the product. The current regulatory environment with its "AR," "CBE-0," "CBE-30," "supplement required," and "compatibility protocol" options already provide the flexibility needed for changes. However, *in practice*, often the changes made not only do **not** improve product quality but also have the effect of actually reducing one or more of the critical quality characteristics of the product. Thus this guidance should make it clear that a quality system's approach does **not** permit any change that reduces any aspect of quality of the product. Also, this guidance needs to make it crystal clear that statistical control tracking and trending techniques should be used in any quality system's approach that is applicable to pharmaceutical manufacturing.]

"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.

This reviewer does not agree with the commenter here.

This is the case because the scope of the "all" is clearly limited to "procedures related to production, maintenance, and review of associated records."

"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."

This reviewer agrees with the commenter here but, *since QA may only oversee such evaluations in some firms (because, for example, corporate statisticians do the trend analysis evaluations)*, this reviewer recommends changing the text in question to "... overseeing trend analysis evaluations."

"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."

Rather than the commenter's proposed "reviewing and approving ...," this reviewer recommends simply using the word "overseeing the investigation of ..."

The commenter's addition, "and authorizing product release," should not be made because that issue was addressed in the previous bullet.

However, a sentence such as, "In some firms, QA also determines the acceptability of each batch or lot for release," should be added because this is the reality in some firms.

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

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While this reviewer supports adding this bullet, he would revise its wording to read, "Ensuring a CGMP-compliant 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 21 CFR § 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.

While this reviewer agrees in principle with the commenter's suggested changes and the rationale stated for changes, this reviewer would recommend the following alternative:

"Although the staffing number ~~may~~ should be reflective of the size of the operation, the number of individuals assigned to the quality unit ~~should~~ must be sufficient to meet the requirements of 21 CFR § 211.22 and other applicable regulations. The quality unit is accountable for ~~implementing~~ approving, reviewing, and overseeing the implementation of all the controls, and ~~reviewing results of manufacture to ensure~~ for ensuring that product quality standards have been met.

The changes in the first sentence are made to clarify the reality that adequate staffing is a must.

The changes in the second sentence are suggested to align the statement made with the scope of the quality unit's responsibilities.

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.

This reviewer agrees with the commenter.

**"IV. The Quality System Model**

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

This reviewer leaves it up to the Agency to decide if the value added by again stating ideas that were previously enunciated outweighs their alleged redundancy.

However, this reviewer recommends that these lines should be retained.

"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."

This reviewer does not agree with the commenter's suggestion here but, *in light of the commenter's position*, does suggest that the sentence in question should be revised to read:

"Senior managers set implementation priorities and oversee the development of action plans."

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Since it is clear from the context that this sentence properly address responsibilities reserved to senior managers, all that need be done is to change “develop” into “oversee the development of” to correct the ambiguity in this statement since, in reality, only “(s)enior managers set implementation priorities” because they directly control the firm’s resources – factually, at lower levels, managers set their operational priorities in response to the implementation priorities set by senior management.

“Line 356: Change to ‘...the Agency recommends that senior mangers 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.”

This reviewer agrees with the commenter.

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

This reviewer does not agree with the commenter’s proposal because it takes the bulleted item out of its proper context – the listing of the types of documents that should be provided under this guidance’s “Quality Systems Model.”

However, this reviewer does suggest that, starting with the bulleted item in question, this guidance should be revised to read:

- “● The manufacturer’s ~~policies to~~ directives that implement the quality systems criteria, and the supporting objectives (see IV.A.4.)
- The procedures and other documents needed to establish and maintain the quality system
- The proofs that establish that the quality system meets the requirement minimums of the applicable CGMP regulations.”

To be CGMP compliant, a quality system must meet or exceed all of the applicable CGMP *minimums* (see 21 C.F.R. Sec. 210.1 and 21 C.F.R. Sec. 211.1(a), “The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals”).

Since the CGMP regulations at 21 C.F.R. Sec. 211.160(a) explicitly state:

“The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit,” *and inherent in “establishing” any control is the element of proof*, the manufacturer must have proof that establishes the validity of said controls (*including the quality system itself*).

Moreover, because all “laboratory” controls, and, by inference, all other controls must be proven (21 C.F.R. Sec. 211.160(b)) to be (established) “scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity,” and 21 C.F.R. Sec. 110 (“Sampling and testing of in-process materials and drug products.

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- (a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:
  - (1) Tablet or capsule weight variation;
  - (2) Disintegration time;
  - (3) Adequacy of mixing to assure uniformity and homogeneity;
  - (4) Dissolution time and rate;
  - (5) Clarity, completeness, or pH of solutions.
- (b) Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications.
- (c) In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods.
- (d) Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.”)

these proofs must cover **all** aspects of the manufacturing, processing, packing, or holding of a drug product.

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

This reviewer agrees with this commenter that the first instance of the word “record” should be deleted in the sentence in question.

However, this reviewer suggests that other modifications to the paragraph (Lines 366-377) should be made and suggests the following alternative:

“It is recommended, under a ~~modern~~ quality systems approach, that a formal process be established ~~to submit change requests to~~ *for changes to all directives (e.g., mission, vision and values statements, policies, plans, standard operating procedures, and work instructions) covered by the firm's quality system.* It is also recommended that, when operating under a quality system, manufacturers develop and document ~~record~~ control procedures to complete, secure, protect, and archive records, including data, which act as evidence of operational and quality system activities. This approach is consistent with the CGMP regulations, which require manufacturers to ~~develop and document~~ establish and follow scientifically sound and appropriate written controls for specifications, plans, and procedures (21 CFR Sec. 211.160) that direct operational and quality system ~~activities~~ operations, and to ensure that these directives are accurate, appropriately reviewed and approved, ~~and~~ available for use, and followed (see the CGMP regulations at §§ 211.22 (c) and (d), 211.80(a), 211.100(b),

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211.110(a), 211.113(a) and (b), 211.122(a), 211.125(f), 211.130, 211.142, 211.150, 211.165(c), 211.166(a), and 211.167(a)-(c).”

The word “establish” requires more than “develop” because it carries the denotative requirement of proof of soundness.

In addition, 21 CFR 211.160(a), requires that all such controls must be *scientifically sound and appropriate*.

Finally, the process controls’ requirement *minimum*, “and followed,” also occurs in Sections 211.80(a), 211.100 (b), 211.110(a), 211.113(a) and (b), 122(a), 125(f), 130, 142, 150, 165(c), 166(a), and 167(a) – (c).

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

While this reviewer agrees “the word ‘activities’ ... is too open to interpretation,” this reviewer suggests that the word “operations” is less open to interpretation and a better fit in the context of this sentence than the word “requirements.”

However, this reviewer leaves it up to the Agency to decide whether the word “activities” or “operations” should be used here.

“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.”

This reviewer does not agree with the commenter here.

This is clearly the case because the items listed are factually the minimum that should be considered if a quality system is in place.

“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.”

This reviewer does not agree with the commenter and supports making only a minor change to address the commenter’s stated concerns.

This reviewer suggests the text be simply changed to read:

“When developing and implementing new quality systems, reviews should, in general, take place more frequently than when the system has matured”

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

Since the draft’s text does not suggest that “all review outcomes will result in the examples shown,” this reviewer does not support the unsupported change proposed by this commenter.

Moreover, in this reviewer’s experience, the items listed do typically occur in the review outcomes.

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

This reviewer agrees with the commenter here.

“Line 482: Change to ‘...training programs that may include the...’ All of the items listed may not always be necessary.”

This reviewer cannot support the commenter’s suggestion because, as a developer of CGMP-compliant and quality-system-compliant systems, this reviewer knows that all of the items listed are needed.

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

While this reviewer agrees that the term “supervisory managers” is not included in the Glossary, he sees no need for that term to be so included since “supervisory” is simply an adjective modifier here to the noun, “managers.”

However, in consideration of the concern raised by this commenter, this reviewer suggests that the Agency consider changing the text in question to read:

“When operating in a robust quality system environment, it is important that ~~supervisory~~ operations managers ensure that skills gained from training be incorporated into day-to-day performance.”

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

This reviewer cannot support the commenter’s suggestion here because the change suggested is at odds with CGMP – if all design criteria are not approved by the QCU, the firm is not operating in compliance with the applicable CGMP regulations.

“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.”

While this reviewer agrees with the commenter’s change, this reviewer notes that the commenter overlooked the clear CGMP mandate to properly locate the equipment.

To address this need and address other concern, this reviewer recommends that the paragraph in which this text is found be revised to read:

“According to the CGMP regulations, equipment must be ~~appropriately located,~~ qualified, calibrated, cleaned, ~~and~~ maintained and operated in a state of control ~~to prevent contamination and mix-ups~~ (see §§ 211.63, 211.67, and 211.68). [Note: ~~that~~ The CGMP regulations require a higher standard for calibration and maintenance than most generic quality system models.] The CGMP regulations place as much emphasis on process equipment as on testing equipment (§ 211.42(b)), while ~~most~~ the majority of quality systems focus ~~only more~~ on testing equipment.<sup>12</sup> However, the quality system in

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<sup>12</sup> See, for example, Reference # 5.

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ISO/IEC 17025:1999, though titled, 'General Requirements for the Competence of Testing and Calibration Laboratories,' (Reference 14) provides a general quality system that matches the needs of a pharmaceutical manufacturing operation in which controls, evaluations, and numerical values are critical aspects of the system. It applies to any organization that wants to assure its customers of precision, accuracy and repeatability of results produced. Moreover, ISO/IEC 17025 explicitly addresses facilities and equipment, calibration and maintenance, and all aspects of control and measurement, unlike most other quality systems."

The minor changes proposed in the text and the footnote are offered to improve the grammar and readability of the draft's text.

The added statements are offered because they provide an "out of the box" approach to an ISO-9000-related quality system, ISO/IEC 17025, which does seem to be a good match to the needs of a CGMP-compliant quality system.

"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.

This commenter does not support deleting the sentence in question, but does suggest changing that sentence as it was in this reviewer's preceding remarks.

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

To keep the "terms consistent with the rest of the document" and still address "officers," this reviewer suggests that the proper alternative for "officers" is "senior management."

Though, this reviewer leaves it up to the Agency to decide if a change is needed simply for the sake of being "consistent with the rest of the document," and suggests that the sentence in question be changed to state:

"It is critical in a quality system to ensure that the responsible senior managers (or officers) for the contracting manufacturer understand the specific requirements of the contract."

"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."

This reviewer cannot support this change, because it is clear, from the drug product (finished pharmaceutical) CGMP regulations, that only the drug product firm's QCU has the responsibility for "for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company." [See 21 C.F.R. Sec. 211.22(a).]

Since this is the case, the firm's QCU: a) cannot delegate or redefine this authority in any contract or quality agreement between itself and a contract

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supplier **and b)** remain in compliance with the clear CGMP minimums set forth in 21 C.F.R. Sec. 211.22(a).

Therefore, the commenter's obviously non-CGMP-compliant suggestion should be ignored.

"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.

This reviewer disagrees with the commenter's suggestion because all of the items listed do apply in all cases.

"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.

This reviewer does not agree with the commenter here and recommends retaining the sentences in question and modifying them appropriately as follows:

"Packaging and labeling controls, critical stages in the pharmaceutical manufacturing process, are not specifically addressed in **most** quality systems models. Therefore, the Agency recommends that manufacturers, processors and packers always refer to the packaging and labeling control regulations at 21 CFR 211 Subpart G for their quality systems guidance in these areas."

Even as the sentences are in the draft, there is no "confusion" – the text clearly states that, *for pharmaceutical manufacturers, processors, and packers*, packaging and labeling controls are integral parts of any pharmaceutical quality system.

"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."

This reviewer does not agree with the commenter that the text in Lines 581-589 should be moved.

Instead, this reviewer knows that that test in question should be placed in its own section and changed to read as follows:

***7. Improve Process***

In modern quality systems environments, when new or reengineered processes ~~es~~ steps are developed, it is expected that they will be designed in a controlled manner. A design plan would include authorities and responsibilities; design and development stages; and appropriate review, verification, and validation. If different groups are involved in design and development, the model recommends that responsibilities of the different groups be documented to avoid omission of key duties and ensure that the groups communicate effectively. Plans should be updated when needed during the design process. Prior to implementation of processes (or shipment of a product), a robust quality system will ensure that the process and product will perform as intended. Change controls should be maintained throughout the design and design implementation process."

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This reviewer gave this section the number “7.” to reflect its position in the set of topics discussed and appropriately titled it as “*Improve Process.*”

In addition, this reviewer also revised the text slightly to: **a) properly** place the requirement for control at the level of the process step and **b) ensure** that “change controls” are also maintained throughout the *design implementation* process.

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

This reviewer agrees with the commenter here.

“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.

Since “continuous verification” that “the process is in control” is one form of *ongoing validation* or *maintenance qualification*, this reviewer cannot support the commenter’s proposed change here.

However, *in light of the commenter’s issue*, this reviewer does recommend that the text in question be modified to read:

“With proper design (see section IV.C.1), and reliable mechanisms to transfer process knowledge from development to commercial production, a manufacturer should be able to initially validate a manufacturing, processing or packing process<sup>14</sup> and, depending on the process, use continuous verification, continual conformity assessment, and/or the ongoing qualification of each batch or lot to confirm: **a)** ‘the process is in control’ and **b)** the product is meeting its established specification targets.”

The changes proposed to the sentence beginning “With proper design ...” are suggested to: **a)** recognize that the drug product CGMP regulations apply to the manufacture, processing or packing operations and their outputs that need to be continually proven to be valid **and b)** recognize that, *depending upon whether the process is “continuous” or not*, there are at least two viable approaches that may be used.

“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.”

Neither the Agency (see Reference 10, “Compliance Policy Guide Sec. 130.300, \*FDA Access to Results of Quality Assurance Program Audits and Inspections\*, (CPG 7151.02) [http://www.fda.gov/ora/compliance\\_ref/cpg/cpggenl/cpg130-300.html](http://www.fda.gov/ora/compliance_ref/cpg/cpggenl/cpg130-300.html)) nor this reviewer, *a recognized expert in the areas of quality, CGMP compliance, and validation*, can agree with the commenter’s proposal because it confuses a means to establish that a process is valid, namely, “continuous verification,” with

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<sup>14</sup> See Reference #6.

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expected outcome, the continual “validation” of the process and the drug product it produces.

Based on the preceding, the Agency should again ignore the commenter’s misplaced suggestion in this instance.

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

Since the text in lines 674 to 675 currently reads, “Both the CGMP regulations (see § 211.110) and quality systems models call for the monitoring of critical process parameters during production,” this reviewer sees nothing that needs to be changed.

This commenter’s apparently misplaced request should be ignored.

“Line 677: Change to ‘Critical process steps...’ This will clarify that not all process steps may need to be verified.”

The commenter’s requested change should be ignored.

Factually, *when one uses a quality systems approach*, one must verify the performance of all steps, this reviewer suggests that this comment should be ignored.

Moreover, *from a quality systems viewpoint*, the only steps that are NOT “critical” are those that can and should be deleted from the operational system because they are absolutely unnecessary.

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

Since the current text reads, “Pharmaceutical products must meet their specifications and manufacturing processes must consistently meet their parameters,” all that is needed here is insert the word “critical” – given the subject is “processes,” the insertion of the word “process” after “critical” is unnecessary.

Therefore, this reviewer can only support changing the sentence to state:

“Pharmaceutical products must meet their specifications and manufacturing processes must consistently meet their critical parameters.”

“Line 702: Change to ‘Are data collection methods documented?’ This will clarify the intent of the sentence.”

Though the commenter’s request is, *in the context presented (bolding added for emphasis)*, “When implementing **data collection procedures**, consider the following,” duplicative, this reviewer does not object to the change requested here but suggests the following alternative wording should be used:

“Are the methods for the evaluation of representative samples and data collection properly documented?”

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“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.”

This reviewer cannot support this commenter here because it is not *per se* the “significance” of the change but the *significance of the outcome of the change that is critical*.

In general, based on the firm’s “understanding of the process,” the true outcome can only be determined by “monitoring and evaluating those specific elements that may be affected.”

When implementing a change, determining its effect should be based on monitoring and evaluating those specific elements that may be affected based on understanding of the process.

Moreover, *until the change has been implemented and those specific elements that may be affected have been monitored and evaluated*, a firm cannot determine its “significance.”

However, this reviewer does suggest that rephrasing the sentence will improve its readability and proposes the following alternative:

“When implementing a change, determining its effect should be based on monitoring and evaluating those specific elements that, based on the firm’s understanding of the process, may be affected.”

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

Neither this reviewer nor the clear requirements of the applicable CGMP regulations support the change proposed here by the commenter.

Based on the applicable CGMP minimums, this reviewer recommends changing the sentence in question to state:

“Invalidation of test results should be: **a)** scientifically ~~and statistically~~ sound, **b)** based on an analyst error, method weakness, or equipment failure established from the critical evaluation (investigation) of all the available pertinent information, and **c)** justified. [**Note:** To facilitate the critical evaluation of data, the manufacturer’s laboratory operations (in-house and contract) should establish a system that identifiably links the specific equipment, materials, personnel, method execution steps, and other factors that may affect outcomes to each result value generated.]”

“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.”

This reviewer leaves it up to the Agency as to whether it is better to move this sentence as the commenter suggests or leave it in its current location.

However, to specifically address “storage” – an equally important area, this reviewer recommends revising the current text to state:

“The Agency recommends that, upon the completion of manufacturing and to maintain quality, the manufacturer should consider shipment and storage requirements to meet

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special handling needs (in the case of pharmaceuticals, one example might be refrigeration).

“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.”

In general, this reviewer agrees with the commenter except that the ambiguous word “attributes” (which, in science, is taken to mean those *factors* [*characteristics*] of a product that are qualitative) should be replaced with the comprehensive term “characteristics” (which addresses both “attributes” and “variables” (those *factors* that have characteristics that are quantified because they can be taken to “continuously” vary over some defined range).

In addition, more than just measuring, it is important to ensure the uniformity of the process and the product.

Based on both of the preceding, the sentence should be changed as follows:

“To ensure that a product conforms to requirements and expectations, it is important to ensure the uniformity of the process and the product by evaluating *critical* process parameters and *critical* product characteristics (e.g., specified control parameters [such as pH, hardness, viscosity, and disintegration time], and critical product characteristics [such as uniformity of content, drug release, weight, purity, and strength]) as planned.”

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

While this reviewer agrees with the commenter in part, further changes are needed.

This is the case because “safety” is an aspect of both *process control* and *product acceptability*, and “quality” (which includes “availability”) and “efficacy” are aspects of product acceptability.

Thus, this reviewer recommends changing the sentence in question to state:

If the nonconformity is significant, based on consequences to process ~~efficiency~~-control (in terms of conformance to parameter set-points, safety, efficiency, and yield), and/or product ~~quality, safety, and availability~~-acceptability (in terms of conformance to specifications, safety and efficacy), it is important to evaluate how to prevent recurrence.

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

This reviewer cannot support the commenter’s suggestion.

This is the case because that suggestion violates one of the fundamental auditing tenets of quality systems and is, therefore, anti-quality.

Thus, unless a firm is able to audit its entire quality system on an ongoing basis so that, at least annually, all of its operational units have been audited, that firm not only does not truly have a valid quality system but also cannot validly assess the overall “quality system” that the firm claims to have implemented.

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However, this does not mean that once a year the firm should stop and audit everything – a full audit can be achieved by auditing defined portions of the firms operational activities in, for example, the first 11 months of a year and reserving the last month for a review of and report on the global quality system for that firm.

“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.”

This reviewer does not agree with the commenter and notes that this section is not a section on “Risk Management” but a section on “*Risk Assessment*,” a different topic.

“Line 832: Change ‘reiterative’ to ‘iterative’.”

This reviewer agrees with the commenter, notes that at least two (2) other obvious changes are needed (“an” for the “a” before “iterative” and “risk assessment” for “risk management” because the obvious correct phrase here is “risk assessment,” and suggests the following:

“Since risk assessment is ~~a reiterative~~ an iterative process, the assessment should be repeated if new information is developed that changes the need for, or nature of, the risk ~~management~~ assessment.”

**“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.”

Though this reviewer has no problem with the commenter’s request but does suggest that the text in Lines 892-903 should be revised as follows:

“Specifically, successful quality systems share the following characteristics, each of which have been discussed in detail above:

- ~~Science-based~~ Scientifically sound and appropriate approaches
- Decisions based on an understanding of the intended use of a product
- Proper identification and control of areas of potential process weakness
- Responsive deviation and investigation systems that lead to timely remediation
- Sound methods for assessing and reducing risk.
- Well-defined processes and products, starting from development and extending throughout the life of the process and the product it produces
- Systems for careful analysis of the quality of incoming and in-process materials and the drug product
- Supportive management (philosophically and financially)”

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

This reviewer does not agree with the commenter here.

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The term "management," though it is has more than one definition, is well and properly defined in most dictionaries and should not, therefore, be defined in this guidance just as words with common definitions, such as "different" and "provide," need not be defined.

For similar reasons, this reviewer knows that there is no need to define the term "manager" in this guidance.

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**C-08 Comments By Genentech, Posted 7 December 2004**

Genentech begins by stating:

“Enclosed are comments, provided by Genentech, for the *Draft Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*.

We welcome the FDA’s efforts to update and harmonize cGMP (sic) regulations to the current understanding of quality systems for the manufacturing of human and veterinary drugs, including biologics.

Thank you for providing us the opportunity to comment on this Draft Guidance. We hope that you will find our comments useful and constructive.

**GENERAL COMMENTS**

The following comments are provided by Genentech, Inc. We welcome FDA’s efforts to update and harmonize CGMP regulations to the current understanding of quality systems. In general, this draft guidance provides clarity on the quality system model. Our comments are outlined in the following table.”

Genentech’s reviewed comments are as follows:

<b>Gd Line # &amp; Sec.</b>	<b>FDA Guidance</b>	<b>Genentech’s Comment &amp; Reviewer’s Remarks</b>
362, IV.A.3	The standard of quality that will be used.	Clarification. It would be helpful for FDA to clarify “standard of quality” definition in reference to documenting a quality system. An example would be helpful.  This reviewer leaves it up to the Agency to address this commenter’s request here.
418-420, IV.A.5	When developing and implementing new quality systems, reviews should take place more frequently than when the system has matured. Outside of scheduled reviews, the quality system is typically included as a standing agenda item in general management meetings.	Recommend deleting lines 418-420. This topic is covered on lines 402-407.  This reviewer does not agree with the commenter here because this section of the text provides additional useful guidance.
462	Management is also expected to develop cross-cutting groups...	Replace “cross-cutting” with “cross-functional”  The term “cross-functional” is more appropriate than “crosscutting” because it carries with it no connotation of aggression.
569, IV.C.2.	Packaging and labeling controls, critical stages in the pharmaceutical manufacturing process, are not specifically addressed in quality systems models.	Contradictory to statement on line 94, which states that “ it is important to harmonize the CGMPs to the extent possible with other widely used quality management systems including ISO 9000, non-U.S. pharmaceutical quality management requirements.....” , since 21 CFR 820 does address Labeling and Packaging Control.  This reviewer rejects the commenter’s statement because it confuses “quality system <b>models</b> ” ( <b>bolding</b> added), like ISO 9001, with the device CGMP regulations, which are quality system <b>regulations</b> (QSR) – not a QS <b>model</b> .

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<b>Gd Line # &amp; Sec.</b>	<b>FDA Guidance</b>	<b>Genentech’s Comment &amp; Reviewer’s Remarks</b>
644-648, IV.C.4	In a modern quality system, a design concept established during product development typically matures into a commercial design after process experimentation and progressive modification. Areas of process weakness should be identified, and factors that are influential on critical quality attributes should receive increased scrutiny.	<p>Clarification is recommended for how Design Control aligns with the Pharmaceutical Development Process.</p> <p>This reviewer again finds that the commenter is confusing a Quality System Model or “quality system” with the FDA’s QSR for medical devices which is a specific regulatory “implementation” of the, <i>now superceded</i>, ISO 9001:1994. Further, this reviewer would suggest that, IF this “device” alignment were critical, THEN the Agency would have simply stated that any “control” approach used for finished pharmaceuticals should be aligned with the corresponding “control” approach used for devices. Since the Agency did not so state, this reviewer defers to their judgment that this RESTRICTION was not appropriate in this guidance. Based on this and its previous comments, this commenter needs further study in the area of quality systems and the differences between guidance models and regulatory systems.</p>
677, IV.C.4.	Process steps should be verified using a validated computer system or a second person.	<p>Add to clarify: <b>At a minimum, critical</b> process steps should be verified using a validated computer system or a second person. Non-critical steps should not require verification.</p> <p>This reviewer cannot agree with the commenter’s suggestions here because: <b>a)</b> making the changes suggested by this commenter would render this guidance violative of the applicable CGMP <b>minimums</b> for finished pharmaceuticals where such checks are clearly required and <b>b), under a quality system, the <u>only</u> steps in a process that are “Non-critical” are steps that are NOT in the process.</b> If this commenter has any processes that contain truly “Non-critical” steps, this reviewer suggests that the commenter needs to remove them from those processes.</p>
750, IV.C.5.	(e.g., specific control parameters strength)	<p>Rewording this example would be helpful.</p> <p>This reviewer agrees with the commenter here and suggests the following rewording: “(e.g., specified control parameters [such as, pH, hardness, viscosity, and disintegration time], and critical product characteristics [such as, uniformity of content, drug release, and strength])”</p>
751, IV.C.5.	Discrepancies may be detected during any stage of the process by an employee or during quality control activities.	<p>Recommended to broaden the scope of detected discrepancies to include other quality systems, i.e., automation.</p> <p>This reviewer cannot agree with the commenter here because, as worded, the commenter is confusing a “deviations” with “discrepancies.”</p> <p>Add to clarify: Discrepancy may be detected during any stage of the process by an employee, <b>automation systems</b>, or during quality control activities.”</p> <p>This reviewer cannot support the changes proposed but could suggest and support the following: “Discrepancies may be detected during any stage of the process by an employee <b>or a validated computerized system designed to detect discrepancies</b>, or during quality control activities.”</p>

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<b>Gd Line # &amp; Sec.</b>	<b>FDA Guidance</b>	<b>Genentech’s Comment &amp; Reviewer’s Remarks</b>
, Glossary		<p>Overall comment to glossary terms: the terms defined in this section are too broad and do not specifically relate to how they are referenced within this guidance. Recommendations to terms are listed.</p> <p>And?</p>
1013, Glossary	<p>Continuous Improvement – ongoing activities to evaluate and positively change products, processes, and the quality system to increase effectiveness.</p>	<p>Recommend: ongoing activities to evaluate and positively <b>improve product quality, process reliability and robustness, and/or quality system effectiveness.</b></p> <p>In light of this commenter’s “general comment to glossary terms,” the commenter’s proposed changes are, to say the least, disappointing.</p> <p>How is “positively change” better than “positively <b>improve</b>” – it is not only not better but this reviewer knows that the opposite phrase, “negatively improve,” is nonsensical – are not all positive changes improvements?</p> <p>In this instance, this reviewer finds that the original definition is clearly superior to the one proposed by the commenter and recommends the commenter’s alternative simply be ignored.</p>
1039	<p>Pre-production – drug development phase prior to pilot production.</p>	<p>It is our comment that some companies consider pilot production as a GMP (sic) process and other companies consider it to be prior to GMP (sic) production. A clarification of the term “pilot production” will be helpful.</p> <p>In this reviewer’s experience, those who use the acronym “GMP” (sic) when the correct acronym is “CGMP,” and the guidance only speaks to “CGMP,” have CGMP-compliance problems beyond those that any clarification here could address.</p> <p>Further, under the Quality System Model outlined, design is where the model starts and, by statute, CGMP kicks in whenever the drug is administered to man or, for veterinary drug products, the target animal, it is or should be obvious, <i>to those who have the requisite CGMP credentials</i>, that “pilot production” is any, <i>usually small-scale</i>, production of the <i>drug product</i> for administration to man or, for veterinary drugs, the targeted animal species.</p> <p>If the Agency sees the need, this reviewer would recommend that the Agency so define the term “pilot production.”</p>
1041	<p>Preventive Action - Action taken to eliminate the cause of a potential non-conformity, defect, or other undesirable situation to prevent occurrence.</p>	<p>Add: action taken to eliminate the cause of a potential non-conformity, <b>discrepancy</b>, defect, or other undesirable situation to prevent occurrence</p> <p>Since a “<b>discrepancy</b>” is a “non-conformity,” but not all non-conformities are discrepancies, this reviewer sees no need for the commenter’s addition.</p>
1050	<p>Quality Assurance – proactive and retrospective activities that provide confidence that requirements are fulfilled.</p>	<p>Add: proactive and retrospective activities that provide confidence that requirements are fulfilled <b>and the organization with responsibility for such activities.</b></p> <p>This reviewer recommends the commenter’s addition should be changed to read, “, <b>and the organizational unit with the primary responsibility for overseeing such activities.</b>”</p>

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Gd Line # & Sec.	FDA Guidance	Genentech’s Comment & Reviewer’s Remarks
1053	Quality Control – the steps taken during the generation of a product or service to ensure that it meets requirements and that the product or service is reproducible.	<p>Add: the steps taken during the generation of a product or service to ensure that it meets requirements and that the product or service is reproducible <b>and the organization with responsibility for such activities.</b></p> <p>This reviewer finds that, <i>in addition to modifying the commenter’s addition</i>, the basic definition provided should be changed to align it with the expectations of CGMP. Therefore, this reviewer proposes the following text:  <b>“Quality Control</b> – a system of verifying and maintaining a desired level of quality in a product, service or process by careful planning, use of proper equipment, continued inspection, and preventive and corrective action as required, <b>and the organizational unit with the primary responsibility for overseeing said system.”</b></p>
1056	Quality Management – accountability for the successful implementation of the quality system.	<p>Recommend: <b>personnel who are accountable</b> for the successful implementation of the quality system.</p> <p>While this reviewer finds the commenter’s recommendation is an improvement, he suggests the following:  <b>“Quality Management</b> – the organization’s system for, and the <b>personnel who are accountable</b> for, the successful implementation of the firms’ quality system.”</p>
1073	Quality System – .... In the CGMP regulatory context, the quality system establishes the foundation to promote the effective functioning of the five other major systems.	<p>Recommend deleting “in the CGMP regulatory context”</p> <p><b>Quality systems establishes the foundation to promote the effective functioning of the major systems.</b></p> <p>Though this reviewer does not support deleting the phrase “in the CGMP regulatory context” And notes that the commenter’s alternative is grammatically incorrect (subject and verb number agreement) – correctly, “<b>Quality systems establish ...</b>” However, the text in question does need to be modified so that it is not tied to any specific set of operational units as it is in the current text.</p> <p>This reviewer suggests the following:  <b>“Quality System</b> – ... In <del>the</del> a CGMP regulatory context, the quality system establishes the foundation <del>to promote</del> that supports the effective functioning of the <del>five other major systems</del> operational units that fall within the CGMP-compliant Quality System adopted.”</p>
1083	Senior Management – top management officials in a firm who have the authority and responsibility to mobilize resources	<p>Recommend: <b>executive level personnel in firm who have the authority and responsibility to ensure operations and system compliance with CGMP.</b></p> <p>While this reviewer finds that the commenter’s suggestion is an improvement in some ways over the draft’s definition, this reviewer recommends that the text be revised to read:  “top management officials and/or executive personnel in firm who have the authority and responsibility to ensure that the firm has the resources and deploys them in a manner that guarantees its operations, systems, and products fully comply with the applicable statutes, CGMP regulations, and recognized standards.”</p>

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**C-09 Comments By The American Red Cross, Posted 7 December 2004**

The American Red Cross begins by stating:

“The American Red Cross (Red Cross) appreciates this opportunity to provide public comments concerning the Food and Drug Administration’s (FDA or Agency) draft guidance entitled “Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations” (Hereafter, referred to as “the Draft Guidance”).

The Red Cross is committed to the safety of donors and patients, and to meeting the best interests of the public we serve. Through its thirty-six Blood Services regions, the Red Cross supplies approximately half of the nation’s blood for transfusion needs. The plasma donated by Red Cross volunteers is recovered from whole blood and further processed or fractionated into plasma derivatives.

The Red Cross fully supports the intent of the Draft Guidance to describe a comprehensive quality system (QS) model that is consistent with current Good Manufacturing Practices (sic) (cGMP [sic]). Red Cross is fully committed to compliance with all applicable regulations and guidances, and strives to utilize quality systems to ensure compliance with cGMP (sic).

Moreover, as part of its compliance efforts, the Red Cross has devoted a significant amount of time and resources to the development of a comprehensive quality systems model. Based on that experience, we offer the following comments for your consideration.”

The American Red Cross’s reviewed comments are as follows:

**“1. Red Cross recommends that FDA clarify the scope of the Draft Guidance**

Section II.C, ‘Scope of the Guidance,’ states that the Draft Guidance ‘applies to manufacturers of drug products (finished pharmaceuticals), including products regulated by the Center for Biologics Evaluation and Research (CBER)...’ Blood and blood products are regulated as both biologics and pharmaceuticals and are subject to 21 CFR Subpart F (Part 600 et. seq.) and 21 CFR Parts 210 and 211. The Draft Guidance contains only one specific reference to blood and blood products, in a footnote regarding CDER and CBER’s inspectional approach (footnote 9). Because the quality system model represents a paradigm shift, it is imperative that the Draft Guidance be as clear as possible. In order to avoid confusion within the blood banking community, and to enable blood establishments to develop robust quality systems, Red Cross recommends that the Draft Guidance provide specific language regarding the applicability of the quality systems model in the blood establishment context.

An example of the need for such clarification is as follows: In section IV. C. 3 of the Draft Guidance, the Agency discusses the need to ensure that all inputs to the manufacturing process are reliable. The Draft Guidance then suggests means by which this can be accomplished, i.e., through verification of a supplier’s COA and audits of the supplier. While this approach is appropriate and relevant for chemical ingredients, containers and closures, it is not applicable to blood establishment evaluation of “input”, e.g., determination of donor suitability.

If the agency determines that these types of issues are too specific for a guidance of general applicability, Red Cross suggests that FDA develop a specific guidance discussing the quality systems approach in blood establishments.

This reviewer leaves these comments for the Agency to address.

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**“2. Red Cross recommends that the FDA clarify the relationship between the Draft Guidance and FDA’s ‘Guideline for Quality Assurance in Blood Establishments.’**

The Guideline for Quality Assurance in Blood Establishments describes the applicable quality assurance activities for manufacturers of blood and blood components. Red Cross believes that FDA should clarify the relationship between this document and the Draft Guidance, and the expectations that FDA has for quality systems in Blood Establishments.

The Draft Guideline describes a model approach to the organization of a quality system, whereas the ‘Guideline for Quality Assurance in Blood Establishments’ describes specific systems that must be in place. Is the Draft Guidance intended to supercede the ‘Guideline for Quality Assurance in Blood Establishments?’ If the two documents are intended to supplement each other, which document governs if there is a conflict?”

In general, this reviewer leaves it to the Agency to clarify the relationships between the guideline in question and, when issued, this guidance.

However, since a true FDA **guideline** is binding on both the Agency and the industry segment, such guidelines have the force of law and govern in the case of a conflict between such guidelines and any issued guidances that address the same areas.

“Since 1999, AABB has encouraged its members to adopt a systems approach comprised of ten quality systems elements (QSEs) that are critical for producing consistent blood and blood components. AABB-accredited facilities, including Red Cross, already have these ten QSEs in place. The AABB approach represents industry consensus within the blood banking community for quality systems for the manufacture of blood and blood components. To avoid confusion in blood establishments, we believe that there should be consistency between FDA’s Draft Guidance and AABB’s quality systems approach.”

This reviewer suggests that the Agency should address the commenter’s concerns.

Perhaps this could be done by: **a)** including a figure, similar to the one in the draft, for the AABB’s “ten QSEs” and **b)** appropriately changing the text in the guidance that is associated with said figure.

**“3. Red Cross recommends that terms defined in the Glossary of the Draft Guideline be reviewed for harmonization with other FDA quality guidelines and documents.**

Red Cross compared terms in the Glossary of the Draft Guideline with terms defined in 21 CFR 820.3; the “Guideline for Quality Assurance in Blood Establishments” mentioned above; and also with terms defined in Red Cross’ Problem Management System which was reviewed and approved by FDA, as examples of documents that contain quality terms. In some instances the definitions are similar, but slightly different. For example, the definition of “non-conformity” that appears in 21 CFR 820.3 and the definitions of “Quality,” “Quality Assurance,” and “Quality Control” that appear in the 1995 Quality Assurance guideline are different from the same terms in the Draft Guideline and may lead to confusion.”

While this reviewer agrees that there are definitional differences among the documents cited, this reviewer sees no confusion *per se*, because each seems to

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be appropriate to the topic being discussed and, *provided the changes to the definitions in this guidance suggested are appropriately made*, the confusion, if any, should be lessened.

Furthermore, if the definitions of the terms in question were universally recognized, with each having a well-understood meaning, then, there would be no need for these to be defined in any guidance – referencing a suitable dictionary would be all that is required.

Since that is not the case, each document should define these terms in a manner that: **a)** is CGMP compliant and **b)** best suits their usage in the document under draft.

Therefore, this reviewer recommends that the Agency not address the commenter's request here.

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**C-10 Comments By Wells & Associates/Quality Hub, Inc. (W&A/QHI),  
Posted 7 December 2004**

W&A/QHI begins by stating:

“This document provides comments and suggestions on the September 29,2004 FDA document entitled the Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. The document was published by FDA as part of the ‘Risk-Based Approach to Pharmaceutical Current Good Manufacturing Practices (cGMP [sic]) for the 21<sup>st</sup> Century initiative’.

I have been involved in compliance, inspections and enforcement from both the agency side and the industry side.

- I worked for FDA for 24 years - between 1976 and 2000. My FDA experience started as a field investigator (doing drug inspections in the Chicago District). My ending FDA position was a branch chief in the CDRH office of Compliance in Rockville, MD. Also at FDA I was the team leader for the Quality System Inspection Technique (QSIT) project

- Since October 2000 I have been an independent consultant. My client base is pharmaceutical, bio-pharmaceutical and medical device companies.

- My specialty is Quality Systems and Good Manufacturing Practices.

At the outset I commend FDA and CDER for issuing the Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations. The document fills a void that has existed in the industry for a long time. It puts the industry on notice that the Drug GMPs (sic) alone can not provide adequate guidance for producing pharmaceuticals in the 21<sup>st</sup> century. The world of quality has evolved greatly since 1976. It is time the FDA acknowledges it to the pharmaceutical industry.

That being said I am providing comments on two distinct topics:

- The process being followed by FDA and CDER to upgrade the industry’s quality systems, and
- The Guidance Document itself.”

W&A/QHI’s reviewed comments are as follows:

“The Process Followed by FDA

My initial comments are about the process being followed by FDA and CDER to establish the quality system requirements. I am disappointed that FDA could not replace the old 1976 Drug GMP (sic) with a new Quality System based GMP (sic) Regulation (21CFR 211) FDA and CDER took the easy way out and published a ‘Guidance’.”

This reviewer is more concerned that the commenter persists in mischaracterizing the current finished pharmaceutical CGMP regulations set forth in 21 C.F.R. Part 211 as “the old 1976 Drug GMP (sic).”

Based on the commenter’s remarks, this reviewer, *having his expertise in the drug, finished pharmaceutical and medical device CGMP as well as in quality, statistics, analysis and control*, understands that this commenter apparently lacks an in-depth understanding in these areas as they apply to the subject of this guidance, a **“Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations.”**

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Factually, the regulations the commenter cites are the current CGMP regulations for finished pharmaceuticals (drug products).

Further, contrary to the commenter’s remarks indicate, the Agency, in accordance with GGP (good guidance practices; 21 C.F.R. Sec. 10.115) has published a draft guidance and is seeking stakeholder input thereto.

“The new FDA guidance is, in your words, ‘approximately organized according to the System Based Inspection Program’. Yet the System Based Inspection Program is an internal FDA Compliance Program - a document designed for FDA compliance officers and field offices. Basing an industry guideline on a compliance program is backwards. The normal FDA rulemaking process (like the one used by CDRH) would be as follows;

- 1) Get industry and FDA to agree on a new Drug GMP (sic) regulation based on a quality system framework - harmonizing to an international standard such as ISO.
- 2) Publish the GMP (sic) regulation in the Federal Register for comments, and eventually in the Code of Federal Regulations (21CFR 211).
- 3) Develop a tool for the field investigators to use for evaluating the industry’s’ compliance to the new GMP (sic) regulation (such as the QSIT Guide)
- 4) Publish a Compliance Program for the FDA to use for providing guidance to FDA field and center staffs for the inspections and administrative/enforcement activities related to the Good Manufacturing Practices (GMP) regulation.”

First, this reviewer searched both the “.pdf” and the “.doc” versions of the published draft guidance using the phrase “approximately organized” and the word “organized,” and found NO instance where either document states “approximately organized according to the System Based Inspection Program.”

**[Note:** When discussing the organization of this guidance, the guidance clearly states:

**“D. Organization of this Draft Guidance**

To provide a reference familiar to industry, the quality systems model described in this guidance is organized — in its major sections — according to the structure of international quality standards. Major sections of the model include the following:

- Management Responsibilities
- Resources
- Manufacturing Operations
- Evaluation Activities” — very different words than this commenter alleged.]

Second, this commenter improperly uses the word “guideline” when the correct word is “guidance.” **[Note:** This is important because true “guidelines” are binding on both the industry and the Agency, whereas, “guidances,” by law, bind neither – they simply offer assistance, to the industry in this case, and explain the general thinking of the Agency at the time they are FINALIZED.]

Third, the commenter continues to use the inappropriate acronym, “GMP,” when, as the guidance’s text clearly indicates, “CGMP” is the appropriate acronym.

**[Note:** The phrase “Good Manufacturing Practices (GMP’s)” is narrowly defined and its proper acronym established in 21 C.F.R. Sec. 26.1(c): “Good Manufacturing Practices (GMP’s). [The United States has clarified its interpretation that under the MRA, paragraph (c)(1) of this section has to be understood as the U.S. definition and paragraph (c)(2) as the EC definition.]

(1) GMP's mean the requirements found in the legislations, regulations, and administrative provisions for methods to be used in, and the facilities or controls to be used for, the manufacturing, processing,

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packing, and/or holding of a drug to assure that such drug meets the requirements as to safety, and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess.

(2) GMP's are that part of quality assurance which ensures that products are consistently produced and controlled to quality standards.

For the purpose of this subpart, GMP's include, therefore, the system whereby the manufacturer receives the specifications of the product and/or process from the marketing authorization/product authorization or license holder or applicant and ensures the product is made in compliance with its specifications (qualified person certification in the EC)."

Based on the preceding realities, this reviewer recommends that the commenter's remarks be discounted because they add nothing to the issues at hand.

"I am aware of the time and resources it would take to publish a new drug GMP (sic). Additionally, politics plays into the equation when FDA attempts to impose a new regulation on industry (as opposed to a guideline). I believe the time and effort are worth spending. The pharmaceutical industry needs a strong and lasting GMP (sic) that will serve to protect the public and assure drug products are made to the highest standards – with active involvement of a quality system in place at the companies.

The right thing to do is publish a new GMP (sic) in the code of federal regulations which will make them legally enforceable in administrative and legal proceedings. It appears that FDA and CDER chose to go the fast route and shortcut the process by going the guideline route to achieve the same (attempted) goal. I am worried the goal will not be achieved. Court challenges to FDA enforcement actions based on the "guideline" are inevitable. They will be costly (as FDA knows from previous court actions based on enforcement of Guidelines) and may actually set the FDA back in the long run. Short term gains may be made but long term enforcement will be lost."

This reviewer again finds that the commenter's remarks here do not address issues in the guidances and should be ignored.

"In the guidance FDA acknowledges that 'The cGMP (sic) regulations do not specifically cover these additional quality elements.'

First, though in reading this document, this reviewer found that the Agency used the proper acronym, CGMP, about 95 times, but in no instance did he find the commenter's quoted text, "The cGMP (sic) regulations do not specifically cover these additional quality elements," using the search phrase "cgmp regulations" without case matching.

Again, this commenter seems to have made up a text passage to fit what the commenter wanted to read.

The closest text in this draft that this reviewer found (using the aforementioned search phrase) was:

"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." – which is a materially different statement.

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Since the commenter's remarks are based on apparently non-existent text and do not directly address any cogent guidance issue, this reviewer recommends that these remarks should also be ignored.

"It further states 'FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.' Since tables are provided in the guidance document listing 'Quality System Elements' and 'Regulatory Citations' it appears the FDA is justifying the new quality system elements as requirements- Review of the tables, however, finds they do not coincide with 21CFR 211 sections as stated, unless one were to make a liberal interpretation of the CFR. Surely this is a loose way to regulate the industry as opposed to the straightforward rulemaking method described earlier."

First, this reviewer thanks the commenter for actually quoting text that exists in the draft guidance.

However, the commenter seems to have confused misunderstand the meaning of the verb "cite" with the meaning of the noun "citation."

The listings in tables cited by the commenter simply list references to 21 CFR Part 211, they do not cite them.

An example of the citing of a regulatory requirement would be, for example, "statistical quality control criteria must be used in the acceptance of each batch or lot of finished pharmaceuticals for release for distribution (21 C.F.R. 211.165(d))."

Thus, the Agency should again simply ignore the commenter's misplaced remarks.

"Comments on the Guidance

Six-System Diagram versus Closed Loop Systems

I am disappointed by FDA's insertion of the drawing entitled 'FIG. I- SIX-SYSTEM INSPECTION APPROACH'. This drawing only solidifies my previous comments that the guidance is based on an inspection tool (the compliance program). The six elements listed are elements needed for product realization - they are not quality system elements. What is needed is a drawing showing where and how quality system elements should be utilized by the industry. My version of the appropriate drawing: "

Review of the FDA drawing shows it falls short of the understanding that what is needed is 'systems' from initial product and process design to metrics on production performance and customer evaluations. Quality systems involve a closed loop process that shows data is evaluated and fed back into the system for the purposes of continuous improvement."

First, this reviewer does not understand how this commenter **confuses** a clearly labeled figure that appears under the draft guidance's "III. CGMPS AND THE CONCEPTS OF MODERN QUALITY SYSTEMS," **as a part of a single section** "G. Six-system Inspection Model," **and that section's text, with** "quality system elements – but it is obvious that the commenter does confuse the two.

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Second, this reviewer does not understand how the commenter confuses operational functions and their quality-related elements (*as depicted in the commenter's figure*) with the clear 4-part model elements ("Management Responsibilities," "Resources," "Manufacturing Operations," and "Evaluation Activities") in the "Quality System Model" proposed – but the commenter also obviously does confuse these.

Based on the preceding realities, the commenter's remarks should again be ignored.

**"Risk Management**

I am concerned that the guidance fails to adequately address the important subject of risk management. The guidance states 'In a manufacturing quality systems environment, risk assessment is used as a tool in the development of product specifications and critical process parameters. Used in conjunction with process understanding, risk assessment helps manage and control change'. Establishing process control parameters based on risk and incorporating risk assessment in change control are indeed bona fide practices.

This reviewer does not support the commenter's concern because this reviewer knows that, *at its core*, "risk management" is an anti-quality approach to risk.

Unlike many industries, the drug industry is supposed to be risk *adverse* because the risks taken can and, *often do*, result in harm and death to those who take, are given, or use pharmaceutical products of all kinds.

Further, from a pro-quality mindset, the umbrella "risk" term is *risk minimization* with *risk identification*, *risk assessment* and *risk avoidance (risk elimination)* being the operational aspects of *risk minimization*.

Based on the preceding realities, this reviewer strongly suggests that the commenter's remarks on "risk management" be ignored.

"The guidance failed, however, to list other areas where risk assessments are needed. One area it is needed is in the evaluation of product and process non-conformities and in implementation of corrective and preventive actions (the CAPA program). Another risk assessment area not listed in the guidance is validation planning and execution (the Validation program). Product process parameters must be established utilizing risk management tools. This goes to both process development for clinical batches and more importantly in the area of design transfer of the product for commercial production. In real life the latter area is a major concern. If the rush to produce the three validation batches is done without consideration of the risks there are serious consequences later."

With respect to the commenter's remarks, the commenter notes the following realities:

1. Since this guidance is not a "risk assessment" guidance, this reviewer sees no compelling need for the Agency to list "other areas where risk assessments are needed" in this guidance.
2. Moreover, the commenter's remarks indicate that he does not truly understand that the drug product CGMP regulations explicit define the limits on the acceptable risks for the process (**see** 21 C.F.R. Sec. 211.110) and the product (**see** 21 C.F.R. Sec. Sec. 165(d)) or that the entire finished

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pharmaceutical CGMP regulations (21 C.F.R. Part 211) upon which all process and process decisions are risk based because the regulated firm is **required** to make lot and batch decisions based on the outcomes observed from the evaluation of lot-shipment-, lot-, or batch- *representative samples*.

3. Contrary to the commenter's view, *unless it is impossible to do so*, "process parameters" must be "**valid**" and statistically "**derived from** previous acceptable **process average and process variability estimates**," as per 21 C.F.R. Sec. 211.110(b) (**bolding** emphasis added for clarity), "**Valid** in-process **specifications** for such characteristics shall be consistent with drug product final specifications and **shall be derived from** previous acceptable **process average and process variability estimates** where possible **and determined by the application of suitable statistical procedures** where appropriate. Examination and testing of samples shall assure that the drug product and in-process material conform to specifications."

Based on the preceding realities, this reviewer again suggests that the Agency ignore the commenter's misplaced remarks.

"Management Controls

On a positive note I am pleased with the Guidance's sections on Management. It is essential that senior management play a major role in assuring adequate and effective quality systems are in place. It may be worth stating in the Guidance that the Food, Drug and Cosmetic Act already places senior management in the role of assuring those quality systems are in place and are robust. The Park decision at the US Supreme Court reiterates the fact that executives are responsible for the company's GMPs (sic) and quality system regardless of whether they had personal knowledge of the GMP (sic) deficiencies. These responsibilities are inherent - even without the Guidance."

Except for the repeated misuse of the "GMP" (sic) acronym and the factual reality that executives are responsible for ensuring that their regulated company fully complies with all applicable regulations, including the applicable CGMP regulations, this reviewer generally supports the commenter's statements.

"Design Controls

One area that was not adequately addressed in the guidance is Design Control. While the guidance does mention design controls, it fails to mention the needed aspects of design control in product development. Design controls, such as those found in 21 CFR 820.30 (medical devices), are needed to ensure discipline is instilled in the development processes. There are specific steps and "gates" that the development process must pass through. These steps should be outlined by FDA and CDER in a formal document. The discipline that design controls provide will assure the public that the pharmaceuticals they consume were derived from adequately designed clinical batches. Design controls are especially needed when transferring drug products from research into production. Without design controls there is a possibility that the drugs transferred from clinical batches to final production are not the same compound - due to inadequate controls in the earlier stages. Design controls should tighten the steps in drug development - with a result being consistency of the drug product and faster times to market."

While this reviewer leaves it up to the Agency to decide if more guidance is needed in the area of "Design Control," this reviewer sees no need for this *quality system* guidance to go much beyond the level of detail currently provided.

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“I would suggest that the design control guidance delineate where FDA believes the regulated process begins. In other words, explain that the Research side of R & D is not FDA regulated, but the Development side is. Record keeping, production of clinical batches and associated quality system issues must be addressed by the guidance. If a state of GMP (sic) compliance is expected in the product development area, it should be clearly explained.”

This reviewer sees no need to address the commenter's remarks here other than to state that perhaps the Agency should reiterate that the Quality System Model presented addresses the product from the beginning of the design stage and that, by statute, CGMP kicks in whenever the drug is administered to man or, for veterinary drug products, the target animal.

Thus, it is, or should be, obvious, *to those who have the requisite CGMP credentials*, that “pilot production,” is any, *usually small-scale*, production of the *drug product* for administration to man or, for veterinary drugs, the targeted animal species, and that compliance is required at this point.

“CAPA and Root Cause Analysis

Another area that the guidance failed to address is root cause analysis. During the handling of nonconformities and the evaluation activity it is essential that investigations be conducted to determine root causes. Corrective actions that follow should be based on the root causes. While it is not always possible to find root causes, every attempt should be made to determine root cause where appropriate. Language should be added to the non-conformity and corrective action sections to explain FDA's position. It is an expectation already that non-conformities (both product and process) be investigated to the root cause level and appropriate corrective actions be done. It is also becoming an expectation that some form of effectiveness verification be done on the corrective actions. FDA should step up to the plate and provide detailed guidance on the expected industry practice in this area.”

Except to state that: **a)** the issues raised by this commenter fall outside the scope of this guidance and **b)** the commenter provides no language for the areas in which he states the FDA needs to explain its position, this reviewer defers to the Agency on how it should address this commenter's remarks by, at some time in the future, providing the appropriate draft guidance that this commenter is requesting in another document.

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**C-11 Comments By GlaxoSmithKline, Posted 7 December 2004**

GlaxoSmithKline begins by stating:

“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.

### **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.”

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GlaxoSmithKline's reviewed comments are as follows:

"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."

Since the commenter's remarks fall outside the scope of this guidance and speak to all the documents issued under the umbrella of the FDA's "21<sup>st</sup> Century initiative," this reviewer suggests that the FDA should consider issuing a separate "21<sup>st</sup> Century initiative" overview document that addresses this commenters concerns should the Agency find that such is needed.

- There are statements throughout the document that refer to nonalignment/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.

Since the commenter's remarks are, at best, cryptic, this reviewer suggests that the Agency ask the commenter to provide specifics before even attempting to change this guidance.

- 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?

Apparently this commenter has visual perception difficulties because the figure clearly shows that the five manufacturing systems fall entirely within the overarching umbrella of the Quality System.

This reviewer would therefore suggest that the Agency "gray" the labels for the subsystems and change the "Quality System" label to a black broader font so that its is perceptually clearer to the reader that the "Quality System" covers the other systems.

Other than the preceding suggestion, this reviewer suggests that the Agency do nothing other than to answer the commenter's question with "no material aspect of the five pharmaceutical manufacturing systems depicted falls outside of the overarching umbrella 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.

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Based on this knowledgeable reviewer's careful review of this draft guidance document, it is clear to this reviewer that either the commenter failed to carefully read the guidance, or does not understand the fundamental precepts of quality systems in general, and/or ignores the clear "Quality System Model" presented by the Agency in this guidance:

"The model (Quality System Model) is organized into four major sections:

- Management Responsibilities
- Resources
- Manufacturing Operations
- Evaluation Activities"

Based on the preceding, this reviewer recommends that the Agency ignore the commenter's less than constructive remarks here.

- 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."

While this reviewer agrees that some additional coverage in the areas of "Holding and Distribution" (21 C.F.R. Subpart H) as well as "Returned and Salvaged Drug Products (21 C.F.R. Subpart K) could be helpful, this reviewer notes that the "need to manage quality throughout the supply chain" falls outside of the "Pharmaceutical CGMP Regulations."

Therefore, this reviewer recommends that the Agency should address the commenter's stated concerns in documents other than this.

- Product release is regarded as a key quality process in the EU but it receives little if any reference within this guidance document."

Since this guidance is intended to address a "**Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**" and product release is but one facet of one (the "**Laboratory Controls System**") of the five operational systems that comprise the systems that fall under the "**Quality System**" umbrella, this reviewer sees no need for the Agency to respond to the general observation that the commenter expresses here

"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?"

This reviewer suggests that the commenter's improperly phrased question should first be revised to address only 21 C.F.R. Parts 210 and 211 as that is the Agency's stated scope (**see II. BACKGROUND AND PURPOSE, C. Scope of the Guidance**).

Then, the suitably revised question would be:

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“Has this ‘**Quality Systems Approach**’ guidance appropriately addressed all of the pharmaceutical CGMP regulations?”

In this reviewer’s view, *except where this reviewer or others have properly recommended small changes in this draft guidance to improve the language used in certain areas*, the guidance provided has appropriately addressed all of the pharmaceutical CGMP regulations.

However, this reviewer leaves it up to the commenter and the Agency to review all of the comments and then decide, what changes or additions are needed to this guidance.

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**“Specific Comments**

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

This reviewer adds his remarks in the appropriate table cell after the commenter’s remarks.

Line Number	Comment & Reviewer’s Remarks	Proposed Change & Reviewer’s Alternative
282-291	<p>This paragraph appears to be a reiteration of what has already been stated II. B. Goal of The Guidance and in II.D. Organization of this Draft Guidance.</p> <p>This reviewer does not agree with the commenter – the texts in question address their title topics; the information is not reiterated.</p>	<p>Paragraph could be deleted unless consensus is that there is value in restating the goals etc.</p> <p>Leave the draft’s text as it is.</p>
366-367	<p>Clarification is required on what is meant by “change request directives”. Is directive meant to relate to the policy content of the quality system?</p> <p>Recognizing that some clarification is needed here but that the commenter has no problem with the use of the word “directives” that occurs two sentences later in the same paragraph, this reviewer supports changing the text in a different manner to ensure that the scope of the word “directives” is clarified.</p>	<p>Alternative wording is suggested as “--- submit request for changes to the content of quality system documents”.</p> <p>Reviewer suggests changing the text to state: “... : submit requests for changes to all directives (e.g., mission, vision and values statements, policies, plans, standard operating procedures, and work instructions) covered by the firm’s quality system.”</p>
368	<p>The sentence “It is also recommended that, when operating...” needs editing to remove the word “record”.</p> <p>This reviewer agrees with the commenter here.</p>	<p>Remove the “record” that comes immediately after “document”.</p>
417	<p>There is no mention of review of performance indicators.</p> <p>This reviewer does not see the need to mention the phrase “performance indicators” at all, much less here, because “The results of audits and other assessments,” “Customer feedback, including complaints,” “The analysis of the data trending results” and “The status of actions to prevent a potential problem or a recurrence” collectively clearly constitute a review of “performance indicators.” However, this reviewer does suggest that this bullet should be revised to explicitly address CGMP compliance.</p>	<p>Reword bullet to read “Quality performance indicators including product performance metrics”.</p> <p>Reword the bullet to state: “● Product characteristics meet both the applicable CGMP minimums and the other customers’ needs”</p>
518	<p>The use of the terms “contract firm” and contracting manufacturer” is confusing</p> <p>This reviewer does not agree with the commenter’s suggestion but does suggest that Lines 518-521 should be modified to make the text in question clearer.</p>	<p>Suggest the use of contract giver and contract acceptor would provide more clarity.</p> <p>Reviewer suggests: “Under a quality system, the product manufacturer ensures that the contracted firm is qualified. The contracted firm’s personnel should be adequately trained and monitored for performance according to their quality system, and the contracted firm’s and contracting manufacturer’s quality standards should not materially conflict.”</p>

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Line Number	Comment & Reviewer’s Remarks	Proposed Change & Reviewer’s Alternative
660	<p>What is meant by an activity that “continues”? This needs to be qualified as the question that springs to mind is for how long?</p> <p>While this reviewer agrees with the commenter that this needs to be qualified, but thinks that the a different phrase would be more appropriate because a product can continue long after the current process has been replaced by another process.</p>	<p>Suggest “continues” is qualified with “throughout the product lifecycle”.</p> <p>This reviewer suggests “continues for as long as that process is used.”</p>
679	<p>The previous sentence is about completing batch production records. The next sentence talks about time limits. Clarification is required on time limits for what?</p> <p>Though this reviewer agrees with the commenter that the text should be made clearer here but suggests that, because the sentence directly references a CGMP regulation, that regulations clarifying phrase should be used. Moreover, the text for the example provided needs to be more informative.</p> <p>To this end, this reviewer suggests the modifications to the text provided ⇒</p>	<p>Amend wording of sentence to clarify the context and that it is “time limits for processing”.</p> <p>“Although time limits for the completion of each phase of production can be established when they are important to the quality of the finished product (CGMP addresses this; see § 211.111), this does not preclude the ability to establish production controls based on in-process parameters that can be based on desired process endpoints measured using real time testing or monitoring apparatus (e.g., blend until the mixture meets, or surpasses, its predetermined minimum uniformity limits vs. blend for 10 minutes).”</p>
702	<p>The bullet “Are collection methods documented” needs clarification.</p> <p>While this reviewer agrees with the commenter here, he suggests that more is needed than just “data” before collection.</p> <p>This is the case because the validity of the data critically depends upon the collection of representative samples.</p> <p>In addition, the introductory text and the next bullet also need to be changed.</p> <p>This reviewer finds that these changes are important because <i>representative sampling</i> is explicitly required by the CGMP regulations.</p>	<p>Add “data” before “collection methods”.</p> <p>This reviewer suggests changing the text passage in question to state: “When implementing sample and data collection procedures, consider the following:</p> <ul style="list-style-type: none"> <li>• Are the methods for the evaluation of representative samples and data collection documented?</li> <li>• When in the production cycle will the samples and data be collected?</li> <li>• ...”</li> </ul>
750	<p>The phrase “(e.g. specified control parameters strength)” is not clear.</p> <p>This reviewer agrees that the example is unclear but suggests more needs to be done because other parts of this sentence are less than clear and/or inaccurate.</p>	<p>It would make sense if “strength” were removed.</p> <p>This reviewer suggests the following modifications to the sentence in Lines 749-750: “To ensure that a product conforms to requirements and expectations, it is important to ensure the uniformity of the process and the product by evaluating critical process parameters and critical product characteristics (e.g., specified control parameters [such as pH, hardness, viscosity, and disintegration time], and critical product characteristics [such as uniformity of content, drug release, and strength]) as planned. ”</p>

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Line Number	Comment & Reviewer’s Remarks	Proposed Change & Reviewer’s Alternative
762	<p>Unclear what is meant by product availability. Is it bioavailability or availability to the customer? Either way efficacy should also be referenced?</p> <p>While this reviewer agrees with the commenter on the need to mention “efficacy,” this reviewer finds that the sentence is inexact and needs to be more comprehensively revised.</p>	<p>Efficacy should be included in the qualifiers to “product”.</p> <p>This reviewer suggests the following modifications to the sentence in Lines 749-750:            “If the nonconformity is significant, based on consequences to process <del>efficiency</del>-control (in terms of conformance to parameter set-points, safety, efficiency, and yield), and/or product <del>quality, safety, and availability</del>-acceptability (in terms of conformance to specifications, safety and efficacy), it is important to evaluate how to prevent recurrence.”</p>
767	<p>“With proper authorization” occurs twice in the sentence.</p> <p>Though the commenter is correct, this reviewer finds that the commenter’s correction cannot be supported because it leaves out a critical option, product rejection, and the commenter’s insertion of the wording “proper,” does really not change the essential reality that the same wording is repeated.            This commenter recommends a different alternative →</p>	<p>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”.</p> <p>“Remedial action may include correcting the nonconformity; or, with proper authorization and documentation, allowing the product to proceed <del>with proper authorization and the problem documented</del>, or, if allowable, using the product for another application; or rejecting the product.”</p>
821	<p>The section is titled “Risk Assessment” but the content of the section is broader than just assessment because it includes risk minimization, etc.</p> <p>This reviewer does NOT agree with the commenter because all that is discussed in this section is “<i>Risk Assessment</i>,” moreover “risk minimization” is NOT explicitly addressed in this section – the consequences of risk assessment are the closest the text comes to mentioning any other topic.</p>	<p>The suggestion to retitle the section as “Risk management” to reflect the scope of the content.</p> <p>This reviewer recommends that the Agency ignore the commenter’s suggestion because it is clearly NOT supported by the text in the section in question.</p>
832	<p>The word “reiterative” implies that you would be just assessing the same risks again and again.</p> <p>This reviewer agrees with the commenter’s observation that the use of “reiterative” is inappropriate when the activity being discussed is obviously an ongoing activity, “risk assessment.” Hopefully, this commenter and the Agency will generalize this realization to the ongoing activity that is labeled “validation” and similarly cease to use the equally inappropriate term “revalidation” when addressing ongoing (“iterative”) validation and the assessments appertaining thereto.</p>	<p>Replace the word “reiterative” with “iterative”.</p> <p>This reviewer fully supports the change suggested by the commenter here but suggests that it be revised to: “Replace the phrase ‘a reiterative’ with the phrase ‘an iterative’ – so that the replacement suggested will be grammatically correct.</p>

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Line Number	Comment & Reviewer’s Remarks	Proposed Change & Reviewer’s Alternative
852	<p>In order to determine corrective actions you need to understand the real or most probable cause of the problem.</p> <p>This reviewer cannot support the commenter’s request because the commenter’s “Root cause analysis” is but one tool in the toolbox that addresses “Data and risk analyses related to operations and quality system processes.” Thus, root cause analysis falls under the bullet in question.</p> <p>Unless the commenter were to propose and provide a listing of all the recognized tools that fall under the aforementioned bullet, this reviewer cannot support elevating “Root cause analysis” to a level that it does not deserve and hopes that the Agency will realize and support this factuality.</p>	<p>“Root cause analysis” should be added as an additional bullet to the list of information sources</p> <p>This reviewer recommends leaving the draft’s text as it is.</p>
871	<p>This section “Promote Improvement” is weak and needs more concrete suggestions for supportive activities.</p> <p>This reviewer finds that the commenter’s suggestion here is less than helpful and ignores the reality that guidance is supposed to support flexibility and not dictate options when the topic being discussed is some important, but minor, aspect of a guidance document.</p> <p>Overall, the guidance provided is sufficient and in keeping with the spirit of the good guidance practices.</p> <p>Moreover, the commenter’s alternative is overly specific and didactic.</p>	<p>Consider the inclusion of activities such as employee suggestion schemes, benchmarking, and self assessment against business models in this section (see following text for section suggestion).</p> <p>This reviewer recommends:</p> <ol style="list-style-type: none"> <li>a. This commenter’s suggestion either be ignored or</li> <li>b. If the Agency feels compelled to revise the text in question, the Agency should use the alternative text proposed by this reviewer (see the revisions suggested in to the commenter’s post-table text).</li> </ol>

“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.”

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For Lines 871-880 in the draft guidance, this reviewer suggests that the commenter's alternative text and the draft's original text be combined to state:

*"6. Promote Improvement*

Management should improve the effectiveness and efficiency of the quality system ~~can be improved through~~ itself by appropriately utilizing the applicable quality activities described in this guidance. Management may choose to use other improvement activities as appropriate. However, it is critical that senior management be involved in the evaluation of this improvement process (section IV.D.3.). In some organizations, the ~~key~~ underlying purpose of the quality management system is to continually drive improvement in all aspects of the firm's operations.

For firm's driven to continually improve all aspects of their business processes, and their outcomes (including the quality of their products and the satisfaction level of all their customers), the observations and recommendations arising from that organization's —

- Nonconformance reports and rejections
- Complaints
- Internal and external audits
- Data and risk analyses related to operations and quality system processes
- CAPA programs
- Management reviews

can be used to guide the firm's improvement plans and programs.

Other sources of improvement ~~could~~ can be from lessons learned from unexpected incidents and from the shared knowledge and experience of people in the organization. Where possible, 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 senior-management activities that ~~will~~ may aid the establishment of a culture of improvement.

Prior to implementation, improvement actions should be ~~assessed for the need for~~ addressed as the firm's change control systems directs.

~~Managers~~ Finally, senior management should consider benchmarking the quality improvement practices of other organizations with the aim of improving their own ~~internal~~ organization's practices."

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**C-12 Comments By American Association for Homecare (AAHomecare),  
Posted 7 December 2004**

American Association for Homecare (AAHomecare) begins by stating:

“The American Association for Homecare (AAHomecare) would like to make the following comments on the “Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations”, Docket No. 2004D-0443. The Notice of Availability for comment on the referenced draft guidance appeared in the Federal Register on October 4,2004 at page 59256. It appears that AAHomecare’s October 8,2004, request to have the agency extend this docket’s comment period for ninety days has not been granted.

AAHomecare represents approximately 3,000 health care providers, manufacturers and suppliers who furnish home health services, rehab and assistive technologies, and durable medical equipment, prosthetics, orthotics, and supplies (DMEPOS) to millions of Medicare and other government and private payors’ beneficiaries. A significant percentage of our members provide medical gases, primarily oxygen (classified as a pharmaceutical subject to 21 CFR Parts 210 and 211 and impacted by the provision of this draft guidance), to respiratory care patients at their residences. AAHomecare will limit its comments to those issues affecting the manufacture and/or distribution of medical gases provided to patients at their residences.

We understand and appreciate the goal and scope of the guidance as stated in sections B and C of the draft guidance, and we totally agree with the overarching philosophy articulated in both the CGMP regulations and quality systems, that quality must be built into the product. Enclosed.”

AAHomecare’s reviewed comments are as follows:

“However, contrary to lines 538 and 539 of the draft guidance that state that the ‘...language...has been tailored to the pharmaceutical manufacturing environment,’ it has not been tailored in our opinion, to account for the uniqueness of many aspects of the medical gas segment of pharmaceutical manufacturing. Throughout the guidance the terms “robust” and “modern” are associated with the words “quality system,” and in line 353 it states, “Implementing a robust quality system can help ensure compliance with regulations.” One could infer, although is not explicitly stated in the guidance, that failure to employ the recommendations put forth in this guidance may hinder ones ability to comply with regulations and that the organization failing to implement them is archaic in its thinking. We recommend that the words “robust” and “modern” be dropped as adjectives for the words “quality system.” If an adjective were deemed necessary, the word “current” would be acceptable.”

In order not to unnecessarily date the guidance provided, this reviewer has no problem eliminating the word “modern” from this guidance, this reviewer not only rejects the elimination of the word “robust” (because this aspect is critical to a CGMP-compliant quality system), and because this word transcends CGMP compliance and carries with it an implied connotation of striving for excellence.

In addition, using the adjective “current,” to modify quality systems as this commenter suggests, adds nothing to the concept since all quality systems are, by definition, current quality systems.

If the Agency thinks that this guidance should be limited to quality systems that simply comply with all applicable CGMP regulations, then, instead of “robust,” this

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reviewer would suggest that the term "CGMP-compliant" be substituted for or used with the word "robust," where the word "robust" is currently used.

"Although granting the extension of the comment period that AAHomecare had requested in its October 8, letter would have permitted us an opportunity for a more thorough review of the guidance, we offer the following comments related to two areas of the draft guidance, (1) The Quality Unit, and (2) Audits.

**1. Quality Unit; Pages 5 and 6 Lines 200 through 238**

In our response to the Docket No. 03D-0165: "Draft Guidance for Industry on the Current Good Manufacturing Practices for Medical Gases" we provided several comments regarding the structure of the Quality Unit which we believe are equally appropriate for the agency's consideration in this guidance.

The Medical Gases draft guidance recommended '...that the Quality Control Unit perform more than a testing function, be independent of the production process, and have both quality assurance and quality control responsibilities.' We proposed that the Medical Gas guidance be modified to, 'A firm may comply with CGMPs by having the Quality Control Unit's function be independent of the production process being reviewed.' Our proposed change was based on the medical gas industry's long standing practice of utilizing qualified manufacturing personnel to perform testing of in-process and final product to ensure established specifications have been met (the quality control function), and utilizing the 'QCU' for among other things record review and approval (the quality assurance function), including review and approval of test results. This practice has historically been accepted provided there are appropriate controls and safeguards to prevent conflict of interest situations (i.e. individuals are not permitted to review their own work.) We propose that lines 204 through 212 of the draft QS Guidance be modified to reflect a similar option."

This reviewer and the applicable CGMP regulations support the commenter's position because, as written, the guidance mischaracterizes the quality control function and improperly characterizes "QC" as a testing unit.

Thus, this reviewer again recommends that Lines 202-212 be changed to state: "Many of the modern 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~~ among the quality control (QC), ~~and~~ quality assurance (QA) and regulatory affairs (RA) functions.

- QC usually consists of assessing the suitability ~~testing~~ of incoming components, containers, closures and labeling, ~~selected~~ critical in-process materials and the finished products to evaluate the performance of the manufacturing process, ~~and~~ to ensure adherence to proper specifications and limits, and to determine the acceptability of each lot or batch for release.
- QA primarily includes the review and approval of all procedures related to production, maintenance, and review of associated records, and auditing, and ~~performing~~ evaluating trend analyses. In some firms, QA also determines the acceptability of each batch or lot for release.
- RA typically acts as the quality function's bi-directional interface between the other quality functions and the FDA."

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This commenter suggests the preceding changes to address the reality that while quality control is supposed to have “(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit” (21 CFR Sec. 211.22(b)), quality control should “have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, ... The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company” (21 CFR Sec.211.22(a)).

This distinction is increasingly important as more and more manufacturers *outsource* their sample evaluation programs to contract laboratories leading to the reality that increasingly such manufacturer's on-site laboratories that report to the QC function do less and less testing.

In addition, this commenter understands that, *given the realities that exist in the structuring of most pharmaceutical companies*, the important agency/manufacturer interface role of regulatory affairs (RA) units needs to be recognized as a part of the quality control unit.

This is the case because RA typically oversees the conduct of agency inspections, files all submission documents and annual reports, and addresses all issues that arise with the agency.

“Lines 234 through 238 of the draft QS Guidance appear to key on the ‘independence’ of the Quality Unit. These lines also discuss the Quality Unit in ‘small operations’. The Medical Gases draft guidance indicates, ‘In a well-structured and well-defined corporate structure, the QCU would be included as a separate unit’, and further states, ‘A small medical gas manufacturer can designate a single individual as the QCU.’ Historically, independence of the QCU in the medical gases arena has meant that the individual performing the QCU (QA) function at the time of its performance is independent of the manufacturing and quality control process he or she is reviewing. Regarding the size of the QCU, we proposed that the Medical Gases draft Guidance state, ‘The size and complexity of a Quality Control Unit varies greatly with the size of the operation and tasks assigned. (Medical gas) manufacturers may operate one or more locations where a single qualified individual may be appropriately designated as the QCU at each location. Other locations may require more than one qualified QCU individual.’ We believe that the size of the manufacturer should not dictate the setup of the QCU. We believe the QCU must be adequately staffed with personnel qualified to perform its operations, and while performing these operations, independence must be maintained. We propose that lines 234 through 238 of the draft QS Guidance be similarly modified.”

While this reviewer has no problems *per se* with the commenter's remarks here, its comments reinforce the need, enunciated by others, to modify the text to make it more generally applicable.

This reviewer again suggests that the text be changed to state:

“Under a robust quality system, the product and process development units, manufacturing units, and the quality unit can remain independent, but still be included in the total concept of producing quality products. ~~In very small operations,~~

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~~a single individual can function as the quality unit. That person is still accountable for implementing all the controls and reviewing results of manufacture to ensure that product quality standards have been met.~~ Although the staffing number should be reflective of the size of the operation, the number of individuals assigned to the quality unit must be sufficient to meet the requirements of 21 CFR § 211.22 and other applicable regulations. The quality unit is accountable for reviewing, approving, and overseeing the implementation of all the controls and ensuring that product quality standards have been met.”

**“2. Conduct Internal Audit; Page 21 Lines 801 through 819 and the table on page 23**

Although we acknowledge the significant benefits of internal audits for larger organizations, including our members with multiple locations, many of our members are small businesses with the owners of the businesses intimately involved in their day-to-day operations. The table on page 23 of the draft guidance infers that there is a regulatory requirement for conducting internal audits as part of the annual review specified in § 211.180(e). We find no specific requirement in the Pharmaceutical CGMP regulation and therefore we recommend the agency remove “Annual Review: § 211.180(e)” from the second row in the Regulatory Citation column in the table on page 23.”

This reviewer does not agree with this commenter for two reasons:

1. The “Annual Review: § 211.180(e)” is an internal audit.
2. The table on page 23 is a guidance table and, because it only lists sections of the CGMP regulations, it does not cite them so that the table listings themselves have no binding effect upon any organization to which the tables may apply.

Thus, the commenter’s remarks should be ignored by the Agency.

“We also disagree with a commenter who has suggested the agency include the concept of third party audit and certification under ‘Evaluation Activities’ in this guidance.”

This reviewer leaves it up to the Agency to address the commenter’s remarks in this instance.

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**C-13 Comments By Abbott Laboratories, Posted 7 December 2004**

Abbott Laboratories begins by stating:

“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.”

Abbott Laboratories' reviewed comments are as follows:

**“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.”

Upon reflection, this reviewer agrees with the commenter that the word “modern” is both not clear as to its meaning.

In addition, the word “modern” is superfluous and should be removed from this guidance or replaced with a more-appropriate adjective.

This reviewer will address the commenter's other remarks here when this reviewer examines the commenter's “specific comments.”

“Finally, terminology is not consistent throughout the document. For example use of the words managers, management, officers, & senior management.”

This reviewer will also address the commenter's “terminology is not consistent throughout the document” issue in those instances where he finds that the apparent inconsistency adversely affects the guidance provided.

However, this reviewer generally finds that the commenter's remarks seem to confuse valid contextual *terminology variation* with *terminology inconsistency*.

**“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.”

This reviewer finds that the commenter's remarks here are, at best, misplaced.

Factually, the Agency appropriately addresses “the current regulatory submission requirements” in other regulations and guidances to which the commenter's remarks here may be appropriate.

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Moreover, the current regulatory environment, with its “AR,” “CBE-0,” “CBE-30,” “supplement required,” and “compatibility protocol” options, already provides clear “regulatory submission requirements” that are explicitly designed to “accommodate improvement” of the type that this commenter is speaking.

Given the preceding, this reviewer sees no need for the Agency to address the commenter’s request here.

**“Harmonization of Guidances/Requirements**

This document is linked to the proposed ICH document referred to as QIO. Since the conceptual areas to be covered in QIO 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.”

While this reviewer has no problem with this commenter’s wishing for a “common international agreement,” this reviewer finds that the fundamental basis differences between the CGMP *minimum* requirements approach embodied in 21 C.F.R. Parts 210 and 211, *as memorialized in 21 C.F.R. 26.1(c)(1)* [“GMP’s mean the requirements found in the legislations, regulations, and administrative provisions for methods to be used in, and the facilities or controls to be used for, the manufacturing, processing, packing, and/or holding of a drug to assure that such drug meets the requirements as to safety, and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess”], and the less rigorous “quality assurance” principles in other regulatory systems such as those of the EC, *as memorialized in 21 C.F.R. 26.1(c)(2)* [“GMP’s are that part of quality assurance which ensures that products are consistently produced and controlled to quality standards. For the purpose of this subpart, GMP’s include, therefore, the system whereby the manufacturer receives the specifications of the product and/or process from the marketing authorization/product authorization or license holder or applicant and ensures the product is made in compliance with its specifications (qualified person certification in the EC)”], preclude the realization of the commenter’s stated desire here.

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

This reviewer finds that the commenter’s remarks here have juxtaposed the proverbial cart and the horse here.

Factually, it is more important that, “to the extent possible,” “we” in the United States align “the other widely used quality management systems including ISO 9000, QSR, and International Pharmaceutical regulations” with the drug and finished pharmaceutical regulations CGMP regulations in 21 C.F.R. Parts 210 and 211, respectively, because firms having pharmaceutical products approved or licensed for sale in the United States are bound to meet all of the applicable US statutory and regulatory requirements including the US statutory CGMP strictures as set forth in 21 U.S.C. 351(a)(2)(B) and CGMP regulatory requirements set forth in Title 21 of the US Code of Federal Regulations (C.F.R.).

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Hopefully, this commenter will, after reading the reviewer's remarks here, better understand and comply with these laws than its words and apparent actions seem to indicate that it currently may be doing.

**“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?”

First, this reviewer agrees that factually there is “currently no guideline on Quality by Design for pharmaceuticals, and no 21 CFR 211 requirement for Design Control.”

Second, since this document is a guidance document, nothing that it suggests beyond the current statutory and regulatory strictures can or will be, *per se*, treatable as “an inspectional expectation.”

However, if a firm adopts a quality system that incorporates this guidance as its basis, compliance with the quality system the firm purports or represents to have implemented is “an inspectional expectation.”

Hopefully, this reviewer's answer has clarified the binding legal “expectation” here with respect to the commenter's question here.

**“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.”

While this reviewer does agree that some sections have more detail than others, he, and apparently many of the other commenters, found NO difficulty following the “document flow.”

Since this document is a guidance document, the commenter's concern vis-à-vis paralleling “existing regulation” is obviously misplaced.

Moreover, this reviewer, who has a documented history ([see http://www.dr-king.com](http://www.dr-king.com)) of having reviewed many draft guidances, finds that the stricture of this draft guidance does, in fact, parallel some of the other drafts this reviewer has formally reviewed as well as other guidances that this reviewer has read.

Based on the preceding factual realities, this reviewer finds that this commenter's general remarks should be ignored by the Agency and anyone who reads this review or the commenter's remarks.

“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).”

Though this reviewer generally had none of the problems with the footnotes that the commenter reports here, this reviewer will address the commenter's remarks here when this reviewer examines the commenter's “specific comments,” if any, that address this concern

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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.”

This reviewer sees no need for the FDA to hold the forums and/or workshops requested because this guidance is for the industry and not the Agency – thus, the Agency will NOT be implementing this guidance, only a firm in the industry may implement it.

Similarly, this reviewer sees no need for the FDA to hold the forums and/or workshops on “how they will be evaluating implementation of this document,” because the CGMP regulations and existing FDA guidance clearly define how the Agency functions with respect to a firm’s operating in conformity to the systems that it claims to be following – if implemented, the FDA is required to audit (inspect) for adherence – IF a firm does NOT want to be so audited for adherence to the quality system it has implemented, THEN that firm need only NOT implement a formal quality system.

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

Since this commenter does not define what it means by “Significant time,” this commenter cannot directly evaluate the validity of the commenter’s statement here.

However, this reviewer has seen firms in other industries become not only become fully compliant with ISO 9001:1994 and ISO 9001:2000 but also be certified by a recognized ISO auditor to be operating in essential compliance with the “ISO 9000” system implemented in less than a year.

Review of the commenter’s **“Specific Comments:”**

Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
24-25	“...Is not intended to place new expectations on manufacturers”	<p>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 (sic) requirement during inspections.</p> <p>The commenter’s concerns are unfounded and no such problems will occur <u>unless</u> a firm claims to have implemented some recommendation in this guidance but, in fact, has misrepresented its practices and is found not to be following a practice bearing on product safety, efficacy, purity and quality that it claims to be following.</p> <p>In addition, this commenter’s failure to notice that the guidance repeatedly (&gt;90 times) uses the proper acronym, CGMP, for “current good manufacturing practice” and no instance where the acronym, “cGMP” (sic), is used, the commenter seems to be, at least subconsciously, conveying the impression that the commenter does not truly support true compliance with all of the applicable CGMP <b>minimums</b>.</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
45-46	Many pharmaceutical manufacturers are implementing comprehensive, modern quality systems and risk management approaches	<p>Change sentence to: Many pharmaceutical manufacturers are implementing comprehensive quality systems and are initiating risk management approaches.</p> <p>Delete the word “modern”.</p> <p>This reviewer agrees with the commenter that the word “modern” should be deleted.</p>
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.	<p>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.</p> <p>First of all, factually, only the reader can “infer” anything from a document – documents are limited to <i>implying</i> a given fact or idea.</p> <p>Second, as written, the document, by using “will allow” instead of “will ensure/assure/guarantee,” <u>clearly</u> does NOT <b>imply</b> “a manufacturer will be in full compliance if a manufacturer operates their quality systems according to the guidance” as the commenter erroneously infers.</p> <p>Given the preceding facts, the rest of the commenter’s remarks should be disregarded because they are based on a false premise.</p> <p>Delete the word “modern”.</p> <p>This reviewer agrees with the commenter that the text “modern,” should be deleted here.</p>
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.</p> <p>This reviewer does not agree that the Agency needs to define “regulatory system to accommodate improvement” because the current system clearly accommodates <b>controlled</b> improvement as it should for a regulated industry</p> <p>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>The commenter’s remarks are outside the scope of this guidance and should be directly addressed to the Agency – factually, the current reporting mechanisms and requirements are well defined and that definition is continually reviewed and, when required, updated.</p> <p>In addition, it is not clear how the phrases “appropriate knowledge and robust quality systems” are defined.</p> <p>These phrases are clearly not defined because it is the responsibility of the regulated firms to demonstrate that the quality systems they define have “appropriate knowledge” and are “robust.”</p> <p>Delete the word “modern”. This reviewer agrees.</p>

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Line # (s)	Guidance Text	Comments & Reviewer's Remarks
115-116	It may also be useful to manufacturers of components used in the manufacture of these products	<p>It is not clear if the scope of this document applies to component manufacturers (suppliers). Delete this sentence.</p> <p>Though it IS clear that the scope of this document does NOT <i>per se</i> apply to component manufacturers, this sentence permits them to use it if it is useful. Therefore, this sentence should be retained!</p> <p>Section IV.C.3 (line #s 591-632), Examine Inputs, describes the requirements for raw material control.</p> <p>Since this remark has nothing directly to do with the usefulness of this guidance for manufacturers of components, it should be ignored.</p>
190	....manufacturing changes (e.g., changes that alter specifications, a critical product attribute or...	<p>Critical product attribute is not defined in the documents glossary. Add definition to Glossary</p> <p>This commenter does NOT support the commenter request for a definition but does suggest that the text here should be modified (to properly reflect what should be the case) as follows:</p> <p>"In addition, certain manufacturing changes (e.g., changes that alter specifications, <del>or</del> or critical product <del>attribute</del> characteristics <del>or</del> including bioavailability) require regulatory filings and prior regulatory approval (§§ 601.12 and 314.70)."</p> <p>Further, since "critical product" characteristics include "bioavailability" and are clearly any <i>characteristics</i> that may, <i>if changed</i>, adversely affect the safety, efficacy, identity, purity or other quality aspect of an intermediate or the drug product as 21 C.F.R. 211.110 clearly indicates.</p> <p>Should the Agency wish to define the phrase suggested in the Glossary, the reviewer's definition should be sufficient.</p>
196-197	Manufacturer is empowered to make changes based on variability of materials used in manufacturing...	<p>Further clarity is needed. Need more detail on how a manufacturer can make changes and what is meant by variability of materials</p> <p>This commenter's request should, if the Agency wishes to address it, be addressed in a guidance document other than this guidance.</p> <p>This is the case because this guidance is intended to address "quality systems" and not the "variability of materials."</p>
251	Compliance program is to be able to assess whether each of the systems is in a state of control.	<p>It is not clear what is meant by desired state of control. Desired state of control is not defined in glossary.</p> <p>Though the text cited here does not contain the phrase "desired state of control," this reviewer notes that the next sentence (Lines 252-253) does contain this phrase. However, unless the Agency plans to define each and every phrase, the commenter's request should be ignored.</p> <p>Clearly, from the context, the desired state of control is the CGMP-compliant one the each FDA-regulated firm chooses to adopt.</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
290-291	FDA regulatory and inspectional coverage will remain focused on specific CGMP regulations.	<p>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.</p> <p>Unless a firm adopts and implements a quality system, the commenter’s concerns are clearly unfounded because compliance with suggested guidance is not binding and the FDA’s inspectorate is clearly aware of this.</p> <p>However, IF a firm implements a formal CGMP-compliant quality system, THEN, when it is found to be deviating from that system, the FDA’s inspectorate should cite the company for their failure to comply with their own self-imposed requirements because, in such circumstances, such failures are obviously CGMP failures.</p>
319-320	Senior managers set implementation priorities and develop action plans.	<p>Delete “senior”. Implementation priorities and action plans are set at various levels of the organization, not only at the senior level.</p> <p>This reviewer does not agree with the commenter’s suggestion here but, <i>in light of the commenter’s position</i>, does suggest that the sentence in question should be revised to read:  “Senior managers set implementation priorities and oversee the development of action plans.”</p> <p>Since it is clear from the context that this sentence properly address responsibilities reserved to senior managers, all that need be done is to change “develop” into “oversee the development of” to correct the ambiguity in this statement because, in reality, only “(s)enior managers set implementation priorities” because they directly control the firm’s resources – factually, at lower levels, managers set their operational priorities in response to the implementation priorities set by senior management.</p>
324	Advocating continual improvement of operations and the quality system.	<p>Add “where appropriate”. Continuous improvement should not be applied to everything, but should be based on need, risk, etc.</p> <p>This reviewer notes that the text does NOT advocate continuous improvement; the guidance correctly states “continual improvement”</p> <p>Based on this reality and the commenter’s misrepresentation of the text, this reviewer recommends that the Agency should NOT change the actual text as the commenter suggests.</p> <p>This is the case because “Advocating continual improvement of operations and the quality system” <i>in everything</i> is one of the fundamental quality tenets for the management function in quality systems.</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
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> <p>In general, this reviewer agrees with the commenter’s suggested change and supporting rationale, but would suggest the commenter’s 2nd sentence be changed to state:            “In a robust quality systems environment, managers should demonstrate strong and visible support for their firm’s global quality system. Managers should have an understanding of all applicable <del>international</del> regulations (US, other country and international) and apply that <del>knowledge</del> insight to ensure the appropriate global implementation of their firm’s quality system throughout the organization (e.g., across multiple sites).”</p> <p>Since this guidance for firms who market drug products in the US, the managers must first understand all applicable US regulations and then any other applicable regulations required by any other nation and/or internationally.</p>
340-341	Senior managers have the responsibility to ensure that the organization’s structure be documented.	<p>Delete “Senior”. This is a management responsibility but may not always be a “senior” management responsibility.</p> <p>In general, this reviewer agrees with the commenter but would revise the text to state:  <del>“Senior managers have</del> Management has the responsibility to ensure that the organization’s structure <del>be</del> is documented.”</p> <p>The word “management” is a better choice here than “Managers” and the verb “is” should be used instead of the verb “may be” (which implies a condition that is optional) because documentation is a clear finished pharmaceutical CGMP requirement <i>minimum</i> and this responsibility is a quality system expectation.</p>
357-358	...design and implement provides clear organizational guidance and facilitates systematic evaluation of issues.	<p>Replace “design and implement” to “review and approve”. Senior management may not directly design and implement.</p> <p>While this reviewer has no problem with the commenter’s suggestion, he suggest that a different change, “that is designed, approved and implemented,” since senior managers have an oversight responsibility and they also may not directly “review and approve” all aspects of the quality system.</p>
363	The manufacturer’s policies to implement the quality systems criteria, and the..	<p>Change “policies” to “requirements”. The requirements may not always be in the form of a policy.</p> <p>While this reviewer agrees with the commenter that “policies” is too restrictive, the commenter’s change, <i>if read in the context of their rationale</i>, boils down to the, at best, trivial “requirements may not always be in the form of a requirement.”</p> <p>This reviewer suggests the following generalized alternative:            “The manufacturer’s directives that implement the quality systems criteria, and the ...”</p>

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Line # (s)	Guidance Text	Comments & Reviewer's Remarks
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.  This reviewer agrees with the commenter here.
370	Quality system activities	Change "activities" to requirements. The word activities is very vague and implies documentation for items that may not be necessary.  While this reviewer agrees that the word "activities" should be changed, this reviewer recommends that it be changed to "operations" because this term is well understood and more obviously limited to documenting items (operational items) for which documentation is required.
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.  This reviewer rejects the commenter's specious remarks concerning <i>vision</i> because is a recognized, well-understood quality system term that is taken to mean "the ability to perceive something not actually visible, as through mental acuteness or keen foresight; as his breadth of <i>vision</i> made this project possible" (Webster's dictionary). Thus, the commenter's unsupported, apparently quality-system-unaware, and ill-advised change should be ignored.  Delete "modern".  This commenter agrees with the commenter here.
385-386	It must be communicated to, ...personnel and contractors (as applicable), and revised as needed.	Change "personnel" to "employees".  This reviewer does not see a compelling need and, <i>because "personnel" is the term the drug product CGMP uses, suggests that the Agency ignore the commenter's suggestion here.</i>
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?  Since all the guidance is doing is enunciating clear quality system objectives vis-à-vis quality, the guidance neither compels nor requires such. However, contrary to the commenter's statements, the CGMP regulations do speak to quality objectives (see 21 C.F.R. 211.160(a)) and the current failure of a firm to have and follow such is already actionable.  Thus, the commenter's remarks here should be ignored.

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
403-404	Under a quality system, senior managers are expected to conduct reviews of the whole quality system according to a planned schedule.	<p>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.</p> <p>The commenter’s rationale statements here are off the mark. In the applicable recognized quality systems, “senior managers are expected to conduct reviews of the whole quality system” <b>at least annually</b>. Recognizing that this may be accomplished by reviewing certain areas at different times, the Agency appropriately added the phrase, “according to a planned schedule.” Thus, the Agency should ignore commenter’s suggested change in this instance.</p>
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).	<p>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.</p> <p>This reviewer suggests the Agency ignore the commenter’s off-the-mark change suggestion here. Though “customer needs” assessments include “customer feedback” (which may include proactive surveys and does certainly include complaints), such assessments extend beyond feedback to the proactive internal evaluation of what a firm can do to better serve the recipients of its products and/or services.</p>
407-417	Under a quality system, the review should consider at least the following: (eight items listed)	<p>Delete this section.</p> <p>The commenter’s unsupported suggestion should be rejected because the section in question accurately provides valuable guidance as to the minimum that a review should consider.</p>
411	Customer feedback, including complaints	<p>Does this mean all customers? Change to Formal customer complaints and feedback.</p> <p>Rhetorically, did this commenter not read Lines 405-406 or has it forgotten what that sentence states? If it did, its question has been addressed. Since customer complaints are part of customer feedback, the grammatically and logically correct text in this section of the drafts should not be changed.</p>
422	Review outcomes typically include:	<p>Change the word “typically” to “may”. Outcomes of management review may vary and typically suggests the points listed usually occur.</p> <p>This reviewer does not agree that “typically” suggests “usually” and notes that, had the Agency thought that such were the “usual” review outcomes, the draft would have stated, “Review outcomes” usually “include:”</p> <p>Based on the preceding realities, this reviewer suggests that the commenter’s remarks should be ignored.</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
474	Under a quality system, continued training is critical...	<p>It is not clear what continual training means. Define.</p> <p>First of all, the commenter has misread the text passage cited because it states, “continued training,” – not “continual training.” Hopefully, the commenter does know what “continued training” is.</p> <p>However, to better align the guidance with the expectations of the CGMP regulations for finished pharmaceuticals vis-à-vis training in CGMP (see 21 C.F.R. Sec 211.25(a) (<b>bolding added for clarity</b>), “...<b>Training</b> in current good manufacturing practice <b>shall be conducted</b> by qualified individuals <b>on a continuing basis</b> and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them”), this reviewer suggests changing “continued” to “<b>continuing</b>.”</p>
489-490	...it is important that supervisory managers ensure that skills gained from training be incorporated into day-to-day performance	<p>Delete the word “supervisory”. Referring to managers is sufficient since the term “supervisory managers” is not used elsewhere in the document.</p> <p>While this reviewer agrees that the term “supervisory managers” is not included in the Glossary, he sees no need for that term to be so included since “supervisory” is simply an adjective modifier here to the noun, “managers.”</p> <p>However, in consideration of the concern raised by this commenter, this reviewer suggests that the Agency consider changing the phrase in question to read, “operations managers:.”</p> <p>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”.</p> <p>Though this reviewer does not agree with the commenter’s changes including the introduction of the undefined term, “re-training,” this reviewer suggests the following alternative: “... it is important that operations managers ensure <del>that re</del>-training is administered at appropriate intervals to ensure that employees skill sets remain <del>current</del> up to date for their current job functions” to address the commenter’s verbalized concerns in a manner that is appropriate for a CGMP-compliant quality system.</p>
494-495	...and manufacturing processes related to the product, are responsible for specific facility and equipment requirements.	<p>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.</p> <p>This reviewer agrees with the commenter that the word “defining” should be inserted between “for” and “specific” in this statement.</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
505-507	The CGMP regulations place as much emphasis on process equipment as on testing equipment (211.42 (b))	<p>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.</p> <p>This reviewer knows of no requirement to delete a sentence in a draft guidance simply because it has an incorrect reference. Since this sentence states a factual reality, this reviewer suggests that the reference should simply be corrected and the sentence revised to read:                      “The CGMP regulations place as much emphasis on process equipment as on testing equipment (21 211 Subpart D— Equipment), ...”                      Hopefully, the Agency will agree that this option is better than proverbially throwing the baby out with the bath water as the commenter suggests.</p>
514-516	Quality systems calls for contracts (quality agreements) that clearly describe the materials or service, quality specifications responsibilities, and communication mechanisms.	<p>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.</p> <p>First, this reviewer sees no need for the clarification of “the term ‘services’” in the context that it is used here – as the commenter’s remarks clearly indicate, the term is understood. In addition, this reviewer rejects the rest of the commenter’s remarks because they do not germane to the specific issue of having the required “contracts (quality agreements).”                      Thus, this reviewer again suggests that the commenter’s remarks here should be ignored.</p>
520-21	...and the contract firm’s and contacting manufacturer’s quality standards should not conflict.	<p>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.</p> <p>This reviewer rejects the commenter’s suggestion because their rationale is based on an irrational extrapolation from “contract firm’s and contacting manufacturer’s quality standards should not conflict” to the commenter’s “It is unreasonable to assume that the contract manufacturers quality standard will be identical to every standard of their contract firms.”                      Since the stated expectation, “quality standards should not conflict,” is a valid expectation in a quality system environment as well as in a CGMP-regulated firm, this statement should not be replaced by one that addresses a different subject – <i>the level of detail that should be provided in a contract</i>.                      However, this reviewer does making a minor change:                      “The contracted firm’s personnel should be adequately trained and monitored for performance according to their quality system, and the contracted firm's and contracting manufacturer’s quality standards should not conflict.”</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
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.	<p>Change officers to “management”. Keeps terminology consistent within the document. Need to clarify what familiar means.</p> <p>To keep the “terms consistent with the rest of the document” and still address “officers,” this reviewer suggests that the proper alternative for “officers” is “senior management.”</p> <p>However, this reviewer leaves it up to the Agency to decide if a change is needed simply for the sake of being “consistent with the rest of the document.”</p> <p>Since this commenter has problem with what the word “familiar” means, this reviewer suggests that the phrase “are familiar with” be replaced with “understand” as follows:</p> <p>“It is critical in a quality system to ensure that the contracting manufacturer’s responsible senior managers (or officers) <del>are familiar with</del> understand the specific requirements of the contracts.”</p>
548	Documenting associated processes will ensure that critical variables are identified.	<p>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.</p> <p>This reviewer suggests that Lines 547-549 should be change to address this issue and the other concerns expressed by the commenter in this row:</p> <p>“211.100). It is important to establish the responsibility for designing or changing products with personnel who understand the manufacturer’s quality systems and the requirement minimums of the applicable CGMP regulations. If quality is to be truly built into a product, the “building in” process must start at the beginning of the product design phase. This is the case because adding quality later is more difficult and costly, and may not be possible to accomplish. Documenting associated processes <del>will</del> should ensure that all critical variables are identified and, to the extent required, properly controlled. This documentation should include.”</p> <p>The changes proposed reflect this commenter’s decades of experience in all phases of the design, development, implementation and control of a process in a manner that ensures the released products meet their quality expectations.</p> <p>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.</p> <p>Formal documentation and approval of the design control process for pharmaceutical products is not standard practice.</p> <p>This reviewer finds that the issues raised by the commenter here are outside of the scope of this guidance and, <i>if at all</i>, the Agency should address them in other documents.</p>
549	This documentation includes:	<p>Change to This documentation “may” include... Since processes and changes vary not all of the items listed may apply.</p> <p>This reviewer does not agree with the commenter here but does suggest that the text be changed as shown in the previous row.</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
577-579	Distinct labels with discriminating features for different products..., should be included to prevent mislabeling and resulting recalls.	<p>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.</p> <p>This reviewer suggests that the commenter’s rant here be ignored because it is misplaced.</p> <p>The requirement for “(d)istinct labels with discriminating features” goes to the issue of building quality into the finished drug product and, <i>contrary to the commenter’s remarks</i>, such labels do aid preventing mix-ups.</p> <p>Moreover, since the verb, “should” is used, the draft guidance states no “requirement.”</p>
581-589		<p>This paragraph seems to be out of place. It appears to be a summary on design. Should go in line 542 - Design &amp; Develop Product and Processes.</p> <p>This reviewer does agree with the commenter that this “paragraph seems to be out of place.”</p> <p>However, this reviewer suggests that this paragraph would be better placed in its own section “7. Improve Process.”</p>
600-601	The quality systems model calls for the verification of the components and services provided by suppliers and contractors.	<p>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.</p> <p>Since consultants are also contractors and suppliers of services, this reviewer finds the commenter’s remarks are, at best, misplaced and, this, should be disregarded.</p> <p>Moreover, the commenter’s “CGMP specifies” allusion to “contractors” seems to be a stretch here since the only reference this reviewer finds to contractors in the applicable drug and finished pharmaceutical CGMP regulations is § 211.56(d), “Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.”</p>
608-609	Sufficient initial tests must be done to establish reliability and to determine a schedule for periodic rechecking.	<p>Need to further clarify what sufficient initial tests means. Also how detailed and how often does periodic retesting have to be?</p> <p>While the commenter’s remarks are misplaced, this reviewer notes that the text in Lines 604-611 must be revised because it misstates what the CGMP regulations actually require.</p> <p>This reviewer suggests that this paragraph be revised to state: “The CGMP regulations require either: a) full testing or b) use of a <del>certificate</del> report of analysis (ROA), commonly called a certificate of analysis (COA) by the industry, <del>plus an identity analysis</del> provided that at least one specific identity test is conducted on such component by the manufacturer, <u>and provided</u> that the manufacturer establishes the reliability of the supplier’s analyses through appropriate validation of the supplier’s test results at appropriate intervals (see §§ 211.22 and 211.84). In the preamble to the CGMP regulations (see comment 239 in the preamble), these requirements were explicitly interpreted. The preamble states that reliability can be validated by conducting tests or examinations and comparing the results to the supplier’s ROA. Sufficient initial tests must be done to establish reliability and to determine a schedule for periodic rechecking.”</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
613	<p>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...</p>	<p>Periodic basis needs further clarification.</p> <p>This reviewer does not agree with the commenter but leaves it up to the Agency to spell out in some other document the Agency’s current expectations regarding the periodic auditing of suppliers.</p> <p>The use of the term “observe” implies that the audit is an on site inspection of the supplier.</p> <p>Since the only way that a manufacturer can determine whether or not a supplier’s facilities are operating in accordance with that supplier’s stated system of manufacture is to visit its site and review that site’s operations. However, since a firm can hire a qualified auditor to act as the firm’s agent (a third-party auditor), the text should be changed to state:</p> <p>“The quality systems approach also calls for the auditing of suppliers on a periodic basis. During the audit, the manufacturer, <i>or its contracted qualified agent</i>, <del>can</del> should observe the testing or examinations conducted by the supplier to help determine the reliability of the supplier’s ROA (COA).”</p> <p>We recommend harmonizing the term, “audit” with that of, “quality audit” as defined in 21 CFR 820.3(t).</p> <p>Though based on the commenter’s remark here, the commenter may have a problem, this reviewer has no problem with “harmonizing the term, ‘audit’ with that of, ‘quality audit’ as defined in 21 CFR 820.3(t)” <u>provided</u> the <i>harmonized</i> definition of “audit” reads:</p> <p>“<i>Audit</i> means a systematic, independent examination of all the systems (quality and operational) of the firm being audited that is performed at defined intervals and at sufficient frequency to determine whether both the firm’s activities and the results of such activities comply with the firm’s implemented procedures for each of said systems, that these procedures are implemented effectively, and that these procedures are suitable to achieve the objectives of all of the firms systems (quality and operational).”</p> <p>Finally, this reviewer notes that this entire section needs other significant changes that this commenter has apparently overlooked for some reason.</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
651-652	...from development to commercial production, a manufacturer should be able to validate the manufacturing process.	<p>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”.</p> <p>Neither this reviewer nor the Agency agrees with the commenter here.</p> <p>This is the case <u>because</u> “continuous verification” that “the process is in control” is one form of <i>ongoing validation or maintenance qualification</i>.</p> <p>However, <i>in light of the commenter’s issue</i>, this reviewer does recommend that the text in Lines 644-652 should be modified to read:</p> <p>“With proper design (see section IV.C.1), and reliable mechanisms to transfer process knowledge from development to commercial production, a manufacturer should be able to initially validate a manufacturing, processing or packing process<sup>14</sup> and, depending on the process, use continuous verification, continual conformity assessment, and/or the ongoing qualification of each batch or lot to confirm: <b>a)</b> ‘the process is in control’ and <b>b)</b> the product is meeting its established specification targets.”</p> <p>The changes proposed to the sentence beginning “With proper design ...” are suggested to recognize that:</p> <ul style="list-style-type: none"> <li><b>a.</b> The drug product CGMP regulations apply to the manufacture, processing or packing operations and their outputs that need to be continually proven to be valid <b>and</b></li> <li><b>b.</b> <i>Depending upon whether the process is “continuous” or not</i>, there are several viable approaches that may be used to assess that the process and the drug product batches are in control.</li> </ul>
658	The entire life cycle should be addressed...	<p>Change to “product life cycle”. Consistency in vocabulary. Line 703 refers to product life cycle.</p> <p>Although the text does need to be changed, this commenter does not agree with the commenter here.</p> <p>This commenter suggests changing the sentence containing this phrase be changed to state:</p> <p>“Although initial commercial batches can provide evidence to support the validity and consistency of the process,<sup>15</sup> <del>the entire life cycle</del> <i>ongoing production</i> should be addressed by the establishment of continuous improvement mechanisms in the quality system.<sup>16</sup>”</p> <p>This reviewer understands that, in this instance, it is the ongoing production (process and product) that “should be addressed by the establishment of continuous improvement mechanisms in the quality system” and not the “<i>entire life-cycle</i>”</p> <p>This is the case <u>because</u> the early phases of the life of the process and the product are <i>obviously beyond the point in time when they can be improved</i>.</p>

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Line # (s)	Guidance Text	Comments & Reviewer’s Remarks
659-660	Thus, in accordance with the quality systems approach, process validation is not a one-time event, but an activity that continues.	<p>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?</p> <p>This reviewer disagrees with the commenter here <u>because</u> the finished pharmaceutical CGMP regulations (21 C.F.R. Part 211) clearly spell out the each-batch requirement for “control procedures ... to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product” (21 C.F.R. 211.110(a)).</p> <p>In addition, the Agency’s recent compliance guide update also addresses the issue of ongoing conformity assessment for each batch and correctly portrays validation as an ongoing journey.</p> <p>Thus, the Agency should ignore the commenter’s remarks here.</p> <p>When would revalidation be necessary? If so, what are the requirements? After any changes or after a specific period of time?</p> <p>Since validation is an ongoing journey, the commenter’s term “revalidation” is, at best, oxymoronic.</p> <p>Based on this reality, the commenter’s remarks here should be disregarded.</p>
674-675	Both the CGMP regulations and quality systems models calls for the monitoring of critical process parameters	<p>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?</p> <p>As the CGMP regulations clearly spell out, a “critical process parameter” is any parameter that requires a control procedure “to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.” (21 C.F.R. Sec. 211.110(a))</p> <p>Under the cited applicable CGMP regulation, all true “CPPs” must be controlled – an activity that cannot be carried out without monitoring all “CPPs.”</p>
677	Process steps should be verified using a validated computer system or a second person.	<p>Add “Critical” process steps... Not all process steps may need to be verified since many steps may not be critical.</p> <p>This reviewer cannot agree with the commenter’s suggestions here because: <b>a)</b> making the changes suggested by this commenter would render this guidance violative of the applicable CGMP <b>minimums</b> for finished pharmaceuticals where such checks are clearly required and <b>b), under a quality system</b>, the <u>only</u> steps in a process that are “Non-critical” are steps that are NOT in the process.</p> <p>If this commenter has any processes that contain truly “Non-critical” steps, this reviewer suggests that the commenter needs to remove them from those processes.</p>

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<b>Line # (s)</b>	<b>Guidance Text</b>	<b>Comments &amp; Reviewer’s Remarks</b>
689-690	...manufacturing processes must consistently meet their parameters.	<p>Add their “critical process” parameters. Since not all parameters may be critical, it is important to keep the focus on those identified as critical.</p> <p>In general, this reviewer agrees with the commenter in this instance but finds that the word “process” is redundant since the subject of here is “manufacturing processes.”</p>
730	Invalidation of test results should be scientifically and statistically...	<p>Define invalidation of test results.</p> <p>To address this commenter’s concern, this reviewer offers the following contextual definition of the term <i>invalidation</i>:            “In a CGMP environment, <i>invalidation</i> means the act or process of proving that something is not valid.”            However, this reviewer leaves it up to the Agency to decide whether or not a formal definition as such should be added to the glossary.</p>

**EMC-03 Comments By Japan Society of Pharmaceutical Machinery and  
Engineering (JSPME), Posted 10 December 2004**

JSPME begins by stating:

“We, the Japan Society of Pharmaceutical Machinery and Engineering (JSPME) are pleased to submit you our offers and comments concerning ‘Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations’ (Docket No. 2004D-0443). We hope that you will consider our comments, and this guidance will be a very fruitful guidance for assuring product quality and ensuring risk management.

We would be much obliged if you give us FDA review of our comments by letter or e-mail.

It is anticipated that this draft ‘Guidance’ in support of a ‘Quality Systems Approach’ will serve as important and very useful guidance for assuring product quality and ensuring risk management. Based on such philosophy, the Japan Society of Pharmaceutical Machinery and Engineering (JSPME) wishes to hereby submit its comments on the draft Guidance. .”

JSPME’s reviewed comments are as follows:

- “1. General: The purpose of this Guidance should be further clarified. Is the Guidance intended to harmonize with other standards such as ISO, or to visualize FDA’s concept described in ‘Pharmaceutical cGMPs (sic) for 21<sup>st</sup> Century: A Risk-Based Approach’?”

Though this reviewer defers to the Agency to address the commenter’s remarks here, this reviewer suggests that the commenter simply carefully reread the guidance’s title, “**Guidance for Industry – Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**” and the first paragraph under “**I. INTRODUCTION**” which states:

“This draft guidance is intended to help manufacturers that are implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211). The guidance describes a *comprehensive quality systems (QS) model*, highlighting the model's consistency with the CGMP regulatory requirements for manufacturing human and veterinary drugs, including biological drug products. The guidance also explains how manufacturers implementing such quality systems can be in full compliance with parts 210 and 211. This guidance is neither intended to place new expectations on manufacturers nor to replace the CGMP requirements. Readers are advised to always refer to parts 210 and 211 to ensure full compliance with the regulations.”

These clearly indicate that the purpose of this guidance is to provide one path for applying recognized *quality system* principals to the CGMP regulations for drugs (21 C.F.R. Part 210) and finished pharmaceuticals (21 C.F.R. Part 211) in a manner that ensures that a firm may, if it so chooses, implement a CGMP-based quality system based on this guidance and still operate in an essential CGMP-compliant manner that meets or exceeds the clear applicable CGMP minimums set forth in 21 C.F.R. Parts 210 and 211.

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- “2. General: The content of the draft Guidance is very similar to that of ISO, particularly in regard to ‘Management Responsibilities’. The document merely makes mention of the difference between cGMP (sic) and the Guidance. Therefore, we suggest that the relationship or differences between the Guidance and standards such as ISO or HACCP, etc., should also be described.”

This reviewer defers to the Agency to address the commenter’s suggestions here.

- “3. General: ‘Management Responsibilities’ for quality systems extend not only to product manufacturing but also areas of pharmaceutical development including non- and clinical studies. From such viewpoint, this Guidance should be higher ranked than cGMP (sic) or other guidance issued to industry.”

Since guidances lack the force of law, the CGMP regulations, *which do carry the force of law*, legally must rank higher than this guidance.

As to its rank versus other guidance issued to the industry, this reviewer again defers to the FDA to address this issue.

However, as the 90+ instances in this guidance seem to indicate, the proper acronym for current good manufacturing practice, as that term is used in the Federal Food, Drug and Cosmetic Act and its codification into statutory code of the United States of America (**see**: 21 U.S.C. Section 351(a)(2)(b)) is “CGMP” — although still widely used by some in the pharmaceutical industry and by some in the FDA, and repeatedly used by this commenter, “cGMP” (sic) is an acronym that should not be used.

CGMP is the correct acronym in the English language because in the statute in which the underlying phrase “current good manufacturing practice” is used all of the words in that phrase have equal weight – 21 U.S.C. Section 352(a)(2)(B) [**bolding** added where the phrase occurs], “a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture

(2)(B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with **current good manufacturing practice** to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;”

Hopefully, after reading this reviewer’s comments and their supporting rationale, this commenter will better understand the reasons for using the acronym CGMP instead of the acronym, “cGMP” (sic), which this commenter has repeatedly used. [**Note**: In this reviewer’s experience with many of the firms in the pharmaceutical industry, it has been this reviewer’s experience that:

1. Those who are **pro quality** use the proper acronym, **CGMP**, for “**current good manufacturing practice**”.
2. Those who are **quality neutral** tend to use the, **cGMP** (sic).
3. Those who are **anti quality** tend use the acronym, **GMP** (sic) – one that is not used in the applicable US statutes and regulations (the closest is the US regulatory acronym **GMP’s** for **Good Manufacturing Practices** as that phrase is

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defined in 21 C.F.R. Part 26 {this Part address “MUTUAL RECOGNITION OF PHARMACEUTICAL GOOD MANUFACTURING PRACTICE REPORTS, MEDICAL DEVICE QUALITY SYSTEM AUDIT REPORTS, AND CERTAIN MEDICAL DEVICE PRODUCT EVALUATION REPORTS: UNITED STATES AND THE EUROPEAN COMMUNITY”}.)

- “4. General: As for example in Lines 604-619, incompatibility exists with other standards such as cGMP (sic). Such inconsistencies should be clarified and resolved, and a procedure for reporting to and involving FDA should be clearly developed and described.”

This reviewer is at a loss to answer the commenter here because, *though the reviewer finds that the paragraphs in question need to be revised*, this reviewer:

1. Finds no fundamental incompatibility between what is said and the **applicable** CGMP regulations that this guidance is intended to address.
2. Has provided alternative wordings to address the minor inconsistencies that this reviewer found:

“The CGMP regulations require either: a) full testing or b) use of a ~~certificate~~ report of analysis (ROA), commonly called a certificate of analysis (COA) by the industry, ~~plus an identity analysis~~ provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (see §§ 211.22 and 211.84). In the preamble to the CGMP regulations (see comment 239 in the preamble), these requirements were explicitly interpreted. The preamble states that reliability can be validated by conducting tests or examinations and comparing the results to the supplier’s ROA. Sufficient initial tests must be done to establish reliability and to determine a schedule for periodic rechecking.

However, if the ROA option is pursued, at least one **specific** identity test is required to be conducted on representative samples of each shipment of each lot (see 21 CFR Sec. 211.84(d)(2) and 21 CFR Sec. 211.160(b)(1)). [Note: The USP’s IDENTIFICATION tests are, in general, **not** identity tests much less specific identity tests and, unless proven to be specific identity tests, cannot be used to comply with 21 CFR Sec. 211.84(d)(2).] Further, to be used for acceptance in lieu of evaluation, the supplier’s ROA must reflect adequate controls for each process critical variable factor (including, for the active pharmaceutical ingredients, the “as is” weight-percent purity) in the manufacturing process or processes in which it is intended to be used and certify that each lot was made in accordance with the applicable CGMP since, by definition, drug components are drugs (see 21 U.S.C. Sec. 321(g)(1)(D)). As an essential element of purchasing controls, it is recommended that data for acceptance and rejection of materials be analyzed for information on supplier performance.<sup>13</sup> In addition, the

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<sup>13</sup> The Agency recommends that manufacturers have a measure of the variability of materials that could affect their process controls. For example, certain changes in physical properties may affect the process, which may affect a finished product’s dissolution characteristics.

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manufacturer’s quality unit is responsible for approving the tests and specifications for all materials (see 21 CFR Sec. 211.22(a)).”

The commenter suggests that the draft’s text should be augmented as changed by this reviewer to ensure that the reader be informed of what the CGMP requirement minimum truly is with respect to the manufacturer’s valid use of the ROA option in lieu of testing the samples sampled.

Specifically, the CGMP requirement *minimums* that:

- each of the *representative samples* sampled from each shipment of each lot **must** be evaluated using a *specific identity test* (and not the USP’s IDENTIFICATION tests [that are **not specific identity tests** and, *in most cases*, are **not even identity tests**]) and
- the CGMP requirement *minimum* that, where appropriate, the ROA **must** report the “as is” weight-percent purity of the component

are clearly delineated.

“The quality systems approach also calls for the auditing of suppliers on a periodic basis. During the audit, the manufacturer, *or its contracted qualified agent*, can observe the testing or examinations conducted by the supplier to help determine the reliability of the supplier’s COA. An audit should also include a systematic examination of the supplier’s quality system to ensure that reliability is maintained. The FDA recommends that a combination approach be used (i.e., verifying the suppliers’ COA through analysis and audits of the supplier). If full analytical testing is not done, the audit should cover the supplier’s analysis. **[Note:** *The collection of representative samples of each shipment of each lot for testing or examination and a specific identity test on each sample collected for testing or examination* ~~is~~ are still required (see § 211.84(b) and § 211.84(d)(2)).]”

Thus, the draft’s text has been changed to reflect the reality that a *specific identity test* on each of the *lot-shipment-representative samples* sampled must be conducted to comply with CGMP and to correct the citation for the *specific identity test* required from the incorrect “§ 211.84(d)(1)” to the correct citation, “§ 211.84(d)(2).”

- “5. General: Quality systems models introduced in this guidance will be the key concept for “Pharmaceutical cGMPs (sic) for 21<sup>st</sup> Century: A Risk-Based Approach” announced on August 2002. However, Lines 118-125 would appear to suggest that the document is not intended to create new expectations, but rather to explain the implementation of comprehensive quality systems. We feel that the necessity for, and/or application of, a quality systems approach should be clearly declared in this document.”

This reviewer is at a loss to address the commenter’s concerns because Part IV of this draft guidance clearly seems to delineate (declare), in detail, the application of a quality systems approach to firms operating under the CGMP for finished pharmaceuticals.

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- “6. Line 116: The scope of this Guidance regarding “manufacturers of components used in the manufacture of these products” should be clarified. For example, is this Guidance applicable for manufacturers producing packaging materials used in PTP or inorganic compounds used in buffer preparation?”

Since this guidance explicitly states, “It may also be useful to manufacturers of components used in the manufacture of these products,” it is up to the manufacturers in question to decide the utility of this guidance for their firms.

If some of the “manufacturers producing packaging materials used in PTP or inorganic compounds used in buffer preparation” find this guidance useable, then they may use this guidance where it is applicable to their operations.

Hopefully, the reviewer’s remarks here have addressed the commenter’s concerns here.

- “7. Lines 169-173: Clear definition of “Risk Management” and “Risk Assessment” should be provided. A description of the two terms is given in Lines 169-173 only.”

This reviewer respectfully disagrees with the commenter here because “Risk Assessment” is defined in Lines 1079-1081, discussed, in some detail, in Lines 821-837, and a pertinent reference (Reference 22) is given in Lines 964-966.

Since “risk management” is, *as it is usually defined*, a management technique that is not aligned with continuous improvement and/or quality excellence, the Agency, *interested in a more quality proactive approach*, correctly only mentioned this subject in passing.

Apparently, sensing that the industry, *including the commenter here*, was not ready for the quality-proactive alternative to “risk management,” “risk minimization,” and also chose not to bring up this topic.

Hopefully, after reading this reviewer’s remarks, the commenter will, at least, have a better understanding of the quality proactive approach to *quality management* and “quality systems.”

- “8. Lines 713-723: Guidance such as SUPAC should be added in ‘Reference’.”

This reviewer leaves it up to the Agency to address the commenter’s request here.

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**EMC-04 Comments By Merck & Company (Merck), Posted 10 December 2004**

Merck begins by stating:

“Merck & Co., Inc. is a leading worldwide, human health products company. Through a combination of the best science and state-of-the-art medicine, Merck's Research and Development (R&D) pipeline has produced many important pharmaceutical products available today. These products have saved the lives of or improved the quality of life for millions of people globally.

Merck & Co., Inc. has vast experience with drug and biological development and manufacturing partnered with the submission and approval of regulatory dossiers worldwide. As such, we welcome the opportunity to provide comment to this draft document intended to encourage the use of quality management system principles. We are encouraged by the FDA's approach of seeing current Good Manufacturing Practice Regulations (cGMP [sic]) as a part of a larger quality system. This along with the Agency's increased focus on using risk assessment in interpreting and applying cGMP (sic) during inspections is very consistent with modern quality systems.

We agree that it is helpful to the pharmaceutical industry to know the regulatory expectations of the quality system initiative. In addition to FDA, there are ICH documents including ICH Q8 (Pharmaceutical Development), ICH Q9 (Risk Management) and possibly ICH Q10 (Quality systems) that are in development. We are supportive of global harmonization of regulatory requirements and expectations and encourage the Agency to continue to foster harmonization.

In addition, we agree with the position of the Pharmaceutical Research and Manufacturers of America (PhRMA) in that the appropriate use of a robust quality system should qualify a manufacturer to make changes in the manufacturing process without seeking approval from the Agency. Therefore, it is of value for those robust quality system requirements to be clearly defined. In addition, we are supportive of the changes suggested by PhRMA and do not see a need to be redundant in a dressing the same points. Therefore, our comments are intended to be in addition to those provided by PhRMA.”

This reviewer notes that this commenter not only apparently knowingly uses the acronym, “cGMP” (sic), but also deliberately and incorrectly defines it as being the acronym for “current Good Manufacturing Practice Regulations (sic) (cGMP [sic])” when, in fact, CGMP is the acronym for “current good manufacturing practice” as that phrase applies to adulterated drugs in 21 U.S.C. 351(a)(2)(B).

Perhaps this is an indication that this commenter's senior management needs additional training in “current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions.” [21 C.F.R. 211.25(a).]

Merck's specific reviewed comments are as follows:

“FDA has in the past used guidance documents, such as this one, to inform both the industry and their investigational staff of new interpretations of existing cGMP (sic) regulations. The use of mandatory language, such as ‘must,’ was used when a particular statement was required by regulation and non-mandatory language, such as ‘should,’ was used to show current Agency thinking while recognizing that other alternatives could also satisfy the intent of the regulation.

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This draft guidance is distinctly different in that it is intended to convey a number of expectations for a broader quality system than is required by cGMP (sic) regulations and changes the use of 'should' to merely suggestions or recommendations if not followed by a regulatory citation (cite).

This reviewer sees that the commenter has apparently mischaracterized this guidance's scope, intent and advice concerning the quality systems approach to the pharmaceutical current good manufacturing practice regulations set forth in 21 C.F.R. Parts 210 and 211 as well as the reach of the underlying key statutory provision (21 U.S.C. Sec. 351(a)(2)(b)) upon which the CGMP regulations rest.

Factually, the Federal Food, Drug, and Cosmetic Act as amended, commonly abbreviated as the "FDC Act," in 21 U.S.C. Sec. 351(a)(2)(B), states:

"Sec. 351. Adulterated drugs and devices

A drug or device shall be deemed to be adulterated--

(a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture

(2) ... (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;

Thus, *though the CGMP regulations set forth in 21 C.F.R. Parts 210 and 211 establish a floor below which it is obvious that a non-complying drug is adulterated, the FDC Act establishes another hurdle* that a manufacturer, processor, packer or holder (as well as, based on 21 C.F.R. Sec. 210.3(b)(12), packager of, labeler of, tester of, and quality controller of drug products) **must meet** for a drug or drug product – such firms must have facilities and controls, and use methods that provably conform to, operate and be administered in conformity with **current good manufacturing practice** (CGMP).

In an era where firms in most other industries are increasingly being operated under some quality system or quality management system, it therefore becomes increasingly difficult for a pharmaceutical firm not to be operated in compliance with a quality system and still claim to comply with the strictures established in 21 U.S.C. 351(a)(2)(B).

The FDA, recognizing this reality, has therefore moved to advise the industry, through this guidance, about one regulation-compliant approach whereby a firm can ensure that it becomes statutorily compliant with CGMP since it is, or should be, obvious to this commenter and others that having a quality system has become or, at the least, is rapidly becoming an integral part of "**current good manufacturing practice**" in the United States of America.

Given the preceding factual reality, this reviewer finds that the commenter's "guidance is distinctly different in that it is intended to convey a number of expectations for a broader quality system than is required by cGMP (sic) regulations and changes the use of 'should' to merely suggestions or recommendations if not followed by a regulatory citation (cite)" is apparently knowingly (as the word, "knowingly" is defined in 21 U.S.C. Sec. 321(bb)(1)) misleading.

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“The draft document has a number of stated expectations that lack a specific regulatory cite, but are nonetheless requirements of cGMPs (sic). In addition, some cGMP (sic) requirements are compounded in sentences with non-cGMP (sic) requirements. The following are specific examples but are not intended to be all inclusive.”

In general, this reviewer finds the commenter’s remarks here both:

- ❖ Instructive (in its continuing “use” of the acronym, “cGMP” (sic), in the face of a guidance that uses the proper acronym, CGMP, more than 90 times in its 20+ pages) and
- ❖ Perplexing (in its distortion of the realities of CGMP as set forth by this reviewer in the reviewer’s preceding commentary).

This reviewer therefore evaluates the specific comments that follow with the preceding context in mind.

“1. Lines 518-521: *‘The firm's personnel should be adequately trained and monitored for performance according to their quality system, and the contract firm's and contracting manufacturer's quality standard should not conflict.’* (No regulatory citation.)”

Comment: The statement that ‘personnel should be adequately trained’ is clearly a regulatory requirement (21 CFR211.25) while the following phrases are suggestions or recommendations.”

This reviewer agrees with the first part of the comment, but must take exception to the second part because, in today’s world, “*the contract firm's and contracting manufacturer's quality standard should not conflict*” is a statutory CGMP expectation for any firm that claims to operate under a CGMP-compliant quality system.

Therefore, the guidance appropriately includes this statement.

“2. Lines 674-683: *‘Both the CGMP regulations (see § 211.110) and quality systems models call for the monitoring of critical process parameters during production.*

- *Process steps should be verified using a validated computer system or a second person. Batch production records should be prepared contemporaneously with each phase of production. Although time limits can be established when they are important to the quality of the finished product (CGMP addresses this, see § 211.115), this does not preclude the ability to establish production controls based on in-process parameters that can be based on desired process endpoints measured using real time testing or monitoring apparatus (e.g., blend until mixed vs. blend for 10 minutes)’.*

Comment: Without regulatory cites for the first two sentences under the above bullet, these should be viewed as only suggestions or recommendations and not as cGMP (sic) requirements or expectations. Some process steps require second person verification or checks. We doubt that FDA investigators would see preparing batch records contemporaneously with each phase of production as being a mere suggestion.”

This reviewer finds the comments here problematic.

The first sentence cited in the comment (“*Process steps should be verified using a validated computer system or a second person*”) is a quality system expectation (that the execution of all actions should be verified) and, in today’s industry, probably

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falls within statutory CGMP – even the commenter admits, “Some process steps require second person verification or checks.”

Second, the commenter’s “*We doubt that FDA investigators would see preparing batch records contemporaneously with each phase of production as being a mere suggestion*” obviously speaks to the reality that the Agency continues to find firms that prepare such records *after the fact* and, *when the FDA does*, the Agency properly records such activities as an observation on that firm’s FDA Form 483.

Oddly, the commentary does not address the last statement quoted here (“*Although time limits can be established when they are important to the quality of the finished product (CGMP addresses this, see § 211.115), this does not preclude the ability to establish production controls based on in-process parameters that can be based on desired process endpoints measured using real time testing or monitoring apparatus (e.g., blend until mixed vs. blend for 10 minutes)*”) even though it also seems to contain a mixture of cited and non-cited statements.

“3. Lines 543-547: ‘*In a modern quality systems manufacturing environment, the significant characteristics of the product being manufactured should be defined, from design to delivery, and control should be exercised over all changes. Quality and manufacturing processes and procedures -and changes to them - should be defined, approved, and controlled (CGMP also requires this; see § 211.100).*’

Comment: It is not always clear as to whether a specific regulatory citation only applies to a specific sentence or whether it may apply to several sentences. This is particularly true when the latter may be viewed as a logical extension of the first. The phrase in the first sentence ‘from design to delivery and control’ is very broad and when seen in conjunction with the second sentence raises questions as how broadly this cited regulation dealing with having written procedures will be interpreted by FDA investigators.”

This reviewer notes that the commenter’s first statement seems to have ignored what the subject that the quoted text is addressing.

Since the subject is a “quality systems manufacturing environment,” it is clear to this reviewer that the quoted text is simply describing aspects of that environment.

Moreover, the parenthetical statement “(CGMP also requires this; see § 211.100)” simply notes that the drug product CGMP requires the suggested “*should be defined, approved, and controlled*” expectations of such quality systems.

Thus, it is clear to this reviewer that the commenter’s lack of clarity is artificial and, by purposely taking the quoted text out of its context (**IV. THE QUALITY SYSTEMS MODEL, C. Manufacturing Operations, 1. Design and Develop Product and Processes**”), a deliberate attempt to muddy the proverbial waters here.

Since taking passages out of context is one of the tools used by persons who have a preconceived conclusion and, by engaging selectively quoting a text that does not necessarily support that conclusion, such persons can easily distort the ideas, precepts, and facts stated in this text, this reviewer: **a)** counsels the Agency to disregard the comments of persons who use this approach **and b)** *though this reviewer does address each of the comments made*, this reviewer generally finds that such comments contain little, if any, valuable insights.

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"4. Lines 623-625: *'Procedures should also be established to encompass the acceptance, use, or the rejection and disposition of materials produced by the facility (e.g., purified water). Systems that produce these in-house materials should be designed, maintained, qualified, and validated where appropriate to ensure the materials meet their acceptance criteria.'*

Comment: Without regulatory cites for the above sentences, these statements would indicate that these are not cGMP (sic) requirements or expectations. However, cGMP (sic) regulations require procedures for these operations. When all cGMP (sic) requirements are not clearly identified, FDA investigators may not know which expectations are viewed as Agency expectations for cGMP (sic) regulations and which are not. "

Because the quoted text has been taken from its context ("IV. THE QUALITY SYSTEMS MODEL, C. Manufacturing Operations, 3. Examine Inputs"), this reviewer, *reading the quoted text in its stated context*, finds that the commenter's first statement seems to be a knowing distortion because, *in that context*, these statements are clearly Quality System "expectations," and the commenter's second statement is almost correct, technically, **the finished pharmaceutical CGMP regulations** do "require procedures for these operations."

However, this reviewer does not share this commenter's hopefully feigned concern because, *as any person trained in the CGMP that is applicable to his or her assigned tasks (as this firm's assigned commenters are required to be)*, FDA investigators should know which are regulatory requirements and which are not such requirements.

Further, *as any knowledgeable compliance person, including the FDA's trained drug "investigators," should*, this reviewer understands:

- The Quality System "expectations" explicitly set forth in this guidance as such "expectations" fall outside of the CGMP "regulations"
- These Quality System "expectations" *probably* are within the statutory scope of CGMP as set forth in 21 U.S.C. Sec. 351(a)(2)(B) because these are generally recognized by today's industries as clear Quality System requirements, and
- All valid Quality System "expectations" *definitely* are within the statutory scope of CGMP as set forth in 21 U.S.C. Sec. 351(a)(2)(B) when a firm formally implements **any** quality system including one based on the Quality System Model set forth in this guidance.

"The draft document has a number of stated 'should' expectations followed by specific regulatory cites indicating that they are cGMP (sic) requirements or expectations. The draft guidance states that it is not intended to create new expectations. However, many of the cited 'should' statements create new expectations and may reasonably be seen by FDA investigators as providing the Agency's current thinking on cGMP (sic) regulations. The following are specific examples but are not intended to be all inclusive"

This reviewer finds that the commenter's statements seem to be intended to further misrepresent this guidance by distorting what the guidance actually states and, *by removing statements from context and excerpting them*, construct

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comments that, *on their face*, seem to be both a reasonable and fair assessment of what the guidance states but, in actuality, are not.

For example, the commenter states, “The draft guidance states that it is not intended to create new expectations,” when, in its overall context, the guidance actually states (**bolding added in some parts of the text for emphasis**):

**“I. INTRODUCTION**

This draft guidance is intended to help manufacturers that are implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211). The guidance describes a *comprehensive quality systems (QS) model*, highlighting the model's consistency with the CGMP regulatory requirements for manufacturing human and veterinary drugs, including biological drug products. The guidance also explains how manufacturers implementing such quality systems can be in full compliance with parts 210 and 211. **This guidance is neither intended to place new expectations on manufacturers nor to replace the CGMP requirements. Readers are advised to always refer to parts 210 and 211 to ensure full compliance with the regulations.**

**FDA’s guidance documents, including this draft guidance, do not establish legally enforceable responsibilities.** Instead, guidances describe the agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. **The use of the word *should* in agency guidances means that something is suggested or recommended, but not required.**

**II. BACKGROUND AND PURPOSE**

**A. Background**

...

**B. Goal of Guidance**

...

**C. Scope of the Guidance**

This guidance applies to manufacturers of drug products (finished pharmaceuticals), including products regulated by the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Veterinary Medicine (CVM). It may also be useful to manufacturers of components used in the manufacture of these products.

**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. Rather, the document explains how implementing comprehensive quality systems can help manufacturers achieve compliance with 21 CFR parts 210 and 211. Although the QS working group found that many of the quality system elements correlate with specific CGMP requirements, some do not. In the end, the Agency expects compliance with the CGMP regulations, and FDA’s inspection program remains geared to compliance with those regulations. ...”**

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Thus, the commenters should have quoted the entire sentence ("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") or, **at least**, all of the first thought conveyed (This document is **not** intended to create new expectations for pharmaceutical manufacturing that go beyond the requirements laid out in the current regulations ...) with an ellipsis ("...") to indicate that the statement was being truncated, but knowingly chose to do otherwise.

Factually, the text, which the commenter distorted, properly implies that this guidance may create "new expectations for pharmaceutical manufacturing" provided said expectations do not "go beyond the requirements laid out in the current regulations ..."

Further the commenter's next statement, "However, many of the cited 'should' statements create new expectations and may reasonably be seen by FDA investigators as providing the Agency's current thinking on cGMP (sic) regulations." is obviously at odds with the guidance's text which clearly states:

"In the end, the Agency expects compliance with the CGMP regulations, and FDA's inspection program remains geared to compliance with those regulations."

Based on the preceding factual realities, the commenter's remarks here (and those that follow) should be either ignored or heavily discounted.

"1. Lines 370-374: *'This approach is consistent with the CGMP regulations, which require manufacturers to develop and document controls for specifications, plans, and procedures that direct operational and quality system activities and to ensure that these directives are accurate, appropriately reviewed and approved, and available for use (see the CGMPs at §§211.22 (c) and (d)).'*

Comment: The inclusion of '*plans*' and '*procedures that direct operational and quality system activities*' are beyond wording in the cited regulation. Both phrases are vague and broad terms making it unclear as to how they might be interpreted by FDA investigators."

"In the context of the Quality Systems Model ("IV. THE QUALITY SYSTEMS MODEL, A. Management Responsibility, 3. Build Your Quality System to Meet Requirements"), the quoted guidance statement is factually correct though the CGMP citation is incomplete.

Instead of correcting the citation, *as a CGMP-knowledgeable organization should have done*, to also include 21 CFR Sections 211.42(c), 211.56(b) & (c), 211.80(a), 211.84(c) & (D)(3), 211.101, 211.110(a) & (b), 211.113(a) & (b), 211.115(a), 211.122(a) & (g), 211.125(c) & (f), 211.130, 211.142, 211.150, 211.160(a) & (b), 211.165(c), 211.167(a)-(c), 211.170(b), 211.176, 211.180(e) & (f), 211.186(b)(9), 211.192, and 211.198(a) and noting that one of the recognized synonyms for the word "*plans*" is "*procedure*," this commenter chose to distort what was the text was stating by:

- Quoting part of the text in a manner that is obviously out of context,
- Leaving out the key phrase "*which require manufacturers to develop and document controls for specifications*," that precedes the word "*plans*" and

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- Deliberating splitting the word “plans” in its comment from the following text, “, and procedures that direct operational and quality system activities,”

this commenter glibly states (**bolding** added to highlight the key word in the commenter’s first statement):

“The inclusion of ‘plans’ and ‘procedures that direct operational and quality system activities’ are beyond wording in the **cited** regulation. Both phrases are vague and broad terms making it unclear as to how they might be interpreted by FDA investigators.”

Though, because of the careful use of the word “**cited**,” the commenter’s first statement is not false on its face; however, it is knowingly misleading.

However, the commenter’s second remark (“Both phrases are vague and broad terms making it unclear as to how they might be interpreted by FDA investigators”) is, at best, a false statement (given the numerous finished pharmaceutical CGMP requirements for “plans” and/or “procedures” [since one of the recognized synonyms for the word “plans” is “procedure,” all of the CGMP citations listed by this reviewer apply to both]) that is not even grammatically correct because the word “plans” is, contrary to the commenter’s view, not a phrase.

Hopefully, *after appraising this reviewer’s remarks and the commenter’s clearly too clever statements here*, the Agency will discount this comment.

“2. Lines 469-472: ‘Personnel should also understand the impact of their activities on the product and the customer (this quality systems parameter is also found in the CGMP regulations, which identify specific qualifications (i.e., education, training, and experience or any combination thereof see §§ 211.25(a) & (b)).’

Comment: The inclusion of ‘also understands the impact of their activities on the product and the customer’ is beyond the wording of the cited regulations. While the cited regulations require personnel to be qualified and familiar with the regulations, it is unclear as to how FDA investigators will interpret this guidance.”

Though this reviewer again must agree that the phrase quoted in the comment is “beyond the wording of the cited regulations,” this reviewer notes that the commenter’s quoted phrase *clearly* falls well within the meaning of the cited regulations (**bolding** added to the quoted text for emphasis):

“§ 211.25 Personnel qualifications.

- (a) **Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions.** Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.
- (b) **Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as**

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**to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.”**

Since the commenter does not propose any text to address the issue that it raises, this reviewer sees no need to amplify further on the commenter's, at best, unnecessary comment.

“3. Lines 497-500: ‘According to CGMP regulations, the QCU has the responsibility of reviewing and approving all initial design criteria and procedures pertaining to facilities and equipment and any subsequent changes (see § 211.22(c)).’

Comment: The inclusion of “*all initial design criteria*” is beyond the wording of the cited regulation. It is unclear as to how FDA investigators will interpret this new expectation. We believe the wording in the regulation allows a company the flexibility as to when Quality's input is most efficient and effective in the development process and that the Quality Unit approval is required for specifications and procedures impacting quality.”

Again, the commenter attempts to focus on the divergence of the guidance from the exact wording of a clearly applicable and encompassing finished pharmaceutical regulation, 21 C.F.R. 211.22(c) in this instance.

Factually, 21 C.F.R. 211.22(c) states (**bolding** added to highlight the key word in this regulation):

“The quality control unit shall have the responsibility for approving or rejecting **all** procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.”

Since “*all initial design criteria and procedures pertaining to facilities and equipment and any subsequent changes*” clearly falls under the stated responsibility “for approving or rejecting **all** procedures or specifications impacting on the identity, strength, quality, and purity of the drug product” and “*all initial design criteria and procedures ...*” clearly can impact “the identity, strength, quality, and purity of the drug product,” the commenter's, at best, misplaced remarks should again be disregarded.

“4. Lines 522-524: ‘However, under the CGMP requirements, the QCU is responsible for approving or rejecting products or services provided under contract (see § 211.22(a)).’

Comment: The exclusion of the word ‘*drug*’ before ‘*products*’ and inclusion of ‘*services*’ expands the scope of the regulation. It is unclear as to whether FDA investigators will include non-drug products or which contracted services will be seen as requiring the Quality control unit approval.”

This reviewer would first note that the commenter's remarks do not challenge the validity of the statement made in the guidance.

In addition, *because the scope of the guidance is limited to drug products*, the commenter's “exclusion of the word ‘*drug*’ before ‘*products*’ ...” is, at best, nitpicking.

Further, the commenter's problem with “*services*” ignores two realities:

- 21 C.F.R. Sec 210.3(b)(12) states, “Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products,” and

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- The commenter's "... and inclusion of '*services*' expands the scope of the regulation" carping ignores two important CGMP realities:
  - said "*services*" are clearly within the scope of the "quality control of drug products," and
  - such "*services*" are clearly within the statutory scope of CGMP (21 U.S.C. Sec. 351(a)(2)(B)).

Based on the preceding, this reviewer again recommends that the Agency simply ignore the commenter's less-than-constructive comments here.

"5. Lines 604-608: 'The CGMP regulations require either testing use of a certificate of analysis (COA) plus an identity analysis (see §§ 211.22 a d 211.84). In the preamble to the CGMP regulations (see comment 239 in the preamble) these requirements were explicitly interpreted. The preamble states that reliability can be validated by conducting tests or examination and comparing the results to the supplier's COA.'

Comment: The cGMP (sic) regulations were paraphrased in a manner that along with discussion could result in FDA investigators interpreting the cGMP (sic) as always requiring testing or a COA on acceptance of supplier material when in fact 21CFR 211.84(a) states 'tested or examined, as appropriate' which provides an alternative to testing when appropriate."

First, this reviewer agrees with the commenter that the cited CGMP regulations were incorrectly paraphrased and again offers the following corrective text:

"The CGMP regulations require either: a) full testing or b) use of a ~~certificate~~ report of analysis (ROA), commonly called a certificate of analysis (COA) by the industry, ~~plus an identity analysis~~ provided that at least one **specific** identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals (see §§ 211.22 and 211.84). In the preamble to the CGMP regulations (see comment 239 in the preamble), these requirements were explicitly interpreted. The preamble states that reliability can be validated by conducting tests or examinations and comparing the results to the supplier's ROA. Sufficient initial tests must be done to establish reliability and to determine a schedule for periodic rechecking.

However, if the ROA option is pursued, at least one **specific** identity test is required to be conducted on representative samples of each shipment of each lot (see 21 CFR Sec. 211.84(d)(2) and 21 CFR Sec. 211.160(b)(1)). [Note: The USP's IDENTIFICATION tests are, in general, **not** identity tests much less specific identity tests and, *unless proven to be specific identity tests*, cannot be used to comply with 21 CFR Sec. 211.84(d)(2).] In addition, to be used for acceptance in lieu of evaluation, the supplier's ROA must reflect adequate controls for each process critical variable factor (including, *for the active pharmaceutical ingredients*, the "as is" weight-percent purity) in the manufacturing process or processes *in which it is* intended to be used and certify that each lot was made in accordance with the applicable CGMP since, by definition, drug components are drugs (see 21 U.S.C. Sec. 321(g)(1)(D)). As an essential element of purchasing controls, it is recommended that data for acceptance and rejection of materials be analyzed for information on supplier

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performance.<sup>13</sup> In addition, the manufacturer's quality unit is responsible for approving the tests and specifications for all materials (see 21 CFR Sec. 211.22(a)).”

“6. Lines 770-771: ‘Customer complaints’ should be handled as discrepancies and be investigated (CGMP addresses this; see § 211.198).’

Lines 1025-1026: Lines 1025-1026: ‘Discrepancy -Datum or result outside of the expected range, an unfulfilled requirement; may be called non-conformity, defect, deviation, out-of-specification, out-of-limit, out-of-trend, etc.’

Comment: The CFR (21CFR211.198(a) states ‘Written procedures...shall include provisions for review...of any complaint involving the possible fail of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation.’ Not all customer complaints are ‘discrepancies’ as defined in the draft guidance and while all complaints must be reviewed or evaluated, not all complaints require investigations.”

Because the quoted text has been taken from its context (“**IV. THE QUALITY SYSTEMS MODEL, C. Manufacturing Operations, 5. Address Nonconformities**”), this reviewer, *reading the quoted text in its stated context*, finds that the commenter’s “Not all customer complaints are discrepancies as defined ...” statement seems to be a knowing distortion because the guidance text quoted “*Customer complaints’ should be handled ...*” does not define “*customer complaints*” as “*discrepancies*,” as the commenter alleges but **only suggests** that, *under the “Quality System Model” presented in this guidance*, how customer complaints should be handled.

Thus, this reviewer recommends that this, at best, off-the-mark comment should simply be disregarded.

“7. Lines 818-819: ‘(FDA's policy is to not routinely review or copy reports and records that result from internal audits per Compliance Policy Guide 130.300)’

Comment: The draft guidance paraphrases the Compliance Policy Guide (CPG) in a manner that may result in FDA investigators believing the Agency policy is to review internal audits as long as such are not routinely done. Actually, the CP states that such inspections of internal audits will not be done during routine inspection and cites only specific instances when such may be done and in practice, a rare occurrence.”

In this reviewer’s experience, FDA investigators are much more aware of what the cited CPG allows and the investigators’ latitude than either this reviewer or the commenter.

Since this is the case, this reviewer simply dismisses this commenter’s attempt to “muddy the waters” concerning what, to this reviewer, is a clear statement that accurately paraphrases the aforesaid CPG.

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<sup>13</sup> The Agency recommends that manufacturers have a measure of the variability of materials that could affect their process controls. For example, certain changes in physical properties may affect the process, which may affect a finished product’s dissolution characteristics.

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“8. Lines 794-795: ‘*Although the annual review required in the CGMP regulations (§ 211.180(e)) call for review of representative batches on an annual basis; quality systems calls for trending on a regular basis.*’

Comment: The cited requirement is for a representative number of batches rather than representative batches. As written, the implication is also that under a broader quality system such trending should be on a ‘regular basis’ rather than annually but offers no indication as whether it should be more or less frequent.”

First the commenter’s correction of the draft’s text “The cited requirement is for a representative number of batches rather than representative batches,” while an improvement, only partially addresses what the applicable drug-product CGMP ***minimum*** is.

The overall drug-product CGMP requirement ***minimum*** set forth in 21 C.F.R Sec 211.180(e) is:

“Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:

- (1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.
- (2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under §211.192 for each drug product.”

Thus, to address the commenter’s real concern for statement accuracy here, this reviewer would recommend that the Agency revise the draft guidance’s text so that it accurately states all of the requirements stated in 21 C.F.R. Sec. 211.180(e).

With respect to the commenter’s concern about the frequency of “*trending on a regular basis,*” this reviewer recommends that this passage be revised to state: “*quality systems call for trending on a regular basis* whose frequency should be tied to the frequency that the firm’s operational systems produce data that should be trended.”

“Merck & Co., Inc. is supportive of FDA's efforts to develop a quality system model for the pharmaceutical industry. However, we have concerns about how this guidance document will be seen by FDA investigators conducting inspections. If FDA moves forward with this document, we suggest that all references to cGMP (sic) regulations be deleted and the guidance clearly state that it is intended only to be a model quality system.”

Since this reviewer finds that the commenter’s concerns are baseless and that the scientifically and/or regulatorily sound, constructive, comments provided by this reviewer and the other commenters more than adequately address the issues that this commenter has raised, this reviewer recommends that the Agency dismiss, with prejudice, the commenter’s unfounded suggestion that “all references to cGMP (sic) regulations be deleted.”

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Since the guidance uses the title, “**IV. THE QUALITY SYSTEMS MODEL**” and uses the word “model” 42 times in reference to this model and (with **bolding** added to identify the contextual usage of the word “model”):

- Starts by stating:

**“I. INTRODUCTION**

This draft guidance is intended to help manufacturers that are implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (21 CFR parts 210 and 211). The **guidance describes a comprehensive quality systems (QS) model, highlighting the model's consistency with the CGMP regulatory requirements for manufacturing human and veterinary drugs, including biological drug products.**”

- Next, under “**II. BACKGROUND AND PURPOSE,**” this guidance states:

**“B. Goal of the Guidance**

**This 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. The **guidance demonstrates** how and where the requirements of the **CGMP regulations fit within** this comprehensive **model.** The inherent flexibility of the CGMP regulations should enable manufacturers to implement a quality system in a form that is appropriate for their specific operations.

- Then, still under “**II. BACKGROUND AND PURPOSE,**” this guidance states:

**“D. Organization of this Draft Guidance**

To provide a reference familiar to industry, **the quality systems model** described in this guidance **is organized** — in its major sections — according to the structure of international quality standards. **Major sections of the model include** the following:

- Management Responsibilities
- Resources
- Manufacturing Operations
- Evaluation Activities”

- Finally, this guidance begins the discussion of this “**QUALITY SYSTEM MODEL**” by stating (**bolding** added to highlight the use of model-centric nature of this guidance):

“The **goal of** this section (“**IV. THE QUALITY SYSTEMS MODEL**”) **is** to describe **a model** for use in pharmaceutical manufacturing that can help achieve compliance with CGMP regulations. It should be noted that implementing an effective quality system in a manufacturing organization will require significant costs in time and resources. However, the long-term benefits of implementing a quality system will outweigh the costs.

**This section describes a robust quality systems model,** which, if implemented, can provide the controls needed to consistently produce a product of acceptable quality. Where applicable, the **relationship between elements of this model** and CGMP regulations is noted,”

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This reviewer suggests that the commenter reread this text and that the Agency ignore the commenter's remarks.

Based on the preceding, this reviewer rejects the commenter's request "the guidance clearly state that it is intended only to be a model quality system" and suggests that the Agency do likewise, because the guidance already clearly states that it presents a "***Quality System***" model, which can be used as one "***Approach***" to the "***Pharmaceutical Current Good Manufacturing Practice Regulations***" for finished pharmaceuticals (drug products), the target of this guidance.

"Further, that while encompassing some of the requirements of the cGMP (sic) regulations, the guidance contains many suggestions and recommendations that go beyond the cGMP (sic) regulations and therefore should not be used during inspections. The pharmaceutical industry will recognize those aspects of the quality system model that are covered by cGMP (sic) regulations and those that are recommended that go beyond cGMP (sic) regulations."

While this reviewer heartily agrees with the commenter that this "guidance contains many suggestions and recommendations that go beyond the cGMP (sic) regulations," this reviewer knows, as does the commenter, WHEN a firm implements a quality system that falls under the statutory reach of CGMP (as defined by 21 U.S.C. Sec. 351(a)(2)(B)), THEN each facility operated by that firm under said quality system is fully subject to inspection by the FDA on an at-least-every-two-years basis.

Furthermore, *to the extent that having a quality system is a recognized aspect of current good manufacturing practice*, and this reviewer knows that this is already the case, under 21 U.S.C. Sec. 351(a)(2)(B), all firms are currently subject to:

- ❖ Inspection for adherence to the fundamental recognized precepts of a quality system and
- ❖ Inspectional observations citing lack of adherence to 21 U.S.C. Sec. 351(a)(2)(B).

Since these are clearly CGMP realities, this reviewer would advise this commenter to abandon its apparently reactive approach to CGMP and, as rapidly as possible, adopt and implement a fully proactive CGMP-fulfilling approach to that CGMP-compliant quality system that best fits its ongoing mission, vision, and values.

Given the facts presented, this reviewer again must recommend the Agency should disregard the commenter's obviously indefensible position here.

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**EMC-05 Comments By Biotechnology Industry Organization (BIO),  
Posted 10 December 2004**

BIO begins by stating:

“The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products. BIO appreciates the opportunity to comment on the Food and Drug Administration's (FDA's, the Agency's) Draft Guidance for Industry on a Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations.”

BIO's reviewed comments are as follows:

**“General Comments**

We support FDA's efforts to refine and update cGMP (sic) regulations and inspectional practices based on changes in technology and business. Development and implementation of effective quality systems are important to the pharmaceutical industry as we move into the 21st century. However while this document may be valuable for a company initially setting up a quality system, it does not provide much additional information for implemented systems.”

This reviewer does not agree with the commenter here and respectfully requests that the commenter carefully reread the draft along with the constructive comments submitted to the docket.

“It is not clear how this document provides clarity regarding interpretation or implementation of cGMP (sic) regulations, or how it provides for a regulatory environment that supports continuous improvement. Therefore, while the draft guidance may be a useful tool for some, it is questionable whether the guidance will have widespread utility for industry as written.”

This reviewer disagrees with the commenter about the guidance's utility and would note that those who begin with the mindset that a tool is not useful tend not to learn how to use that tool at all and, *even when compelled to use it*, seldom learn to use it to best effect.

Since this guidance is not intended to provide “interpretation or implementation of cGMP (sic) regulations,” this reviewer finds the commenter's initial remark, at best, misplaced.

Since providing “a regulatory environment that supports continuous improvement” is corporate responsibility and not the responsibility of any corporate regulator be it the SEC, FCC, FTC, EPA, OSHA, or the FDA, this reviewer must dismisses the commenter's off-target comment; “how” is clearly a corporate business responsibility.

Since the commenter fails to offer any alternatives that address its stated “concerns,” this reviewer must recommend that the Agency ignore the commenter here.

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“There are many points in the guidance where the term “recommends” is used to describe an expectation. Throughout the document it should be clarified what is expected and what is recommended.”

This reviewer leaves it up to the Agency to address this comment because this reviewer sees no need for significant clarifications beyond those that he and others have contributed in the comments to the docket or, in the case of this reviewer, through a review of the e-docket-available comments, in this review that have not been addressed.

**“Specific Comments**

Section I – Line 18 (change). It would be helpful for FDA to define the adjective ‘modern’ as it applies to quality systems or replace with the term ‘effective.’”

Not only is the term’s meaning unclear, as this commenter notes, but also the quality systems upon which this guidance is based have existed for more than a decade and will continue to age.

From this reviewer’s and the views expressed by others, the proper action here would be for the Agency to delete the word “modern” from this guidance wherever it is used as an adjective modifying the phrase “quality system.”

Further, this reviewer finds that the substitution of the adjective “effective” does not improve the guidance in any material manner.

If any “adjective modifier” is needed beyond “robust,” the only generally applicable self-defining adjectives that this reviewer sees may be appropriate in some contexts is the compound adjective “CGMP-compliant” in a regulatory context and “CGMP-conforming” in a statutory context.

However, this reviewer leaves it up to the Agency to address this *de minimus* issue.

“Section II A – Lines 59-60 (clarification). Please reconcile FDA’s intention to use this guidance to supplement the cGMPs (sic) with Quality System requirements as implemented in the medical device area (21CFR820), in contrast to the statement in lines 24-25 that this guidance ‘is not intended to place new expectations on manufacturers.’”

First, contrary to the commenter’s understanding, 21 C.F.R. Part 820 is not a quality system and, though it is a “quality system regulation,” its requirements are explicitly “(c)urrent good manufacturing practice requirements” and not “Quality System requirements.”

Thus, the commenter’s remarks start with a false premise.

Second, as Part 820 clearly states, the requirements set forth are the “basic requirements applicable to manufacturers of finished medical devices” and therefore do not apply to drugs and finished pharmaceuticals (drug products) unless such items are also classified as devices; nor to components or parts of finished devices (“This regulation does not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance.”)

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Specifically 21 C.F.R. 820.1(a) states, in part:

“Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation. The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (the act). This part establishes basic requirements applicable to manufacturers of finished medical devices. If a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged. With respect to class I devices, design controls apply only to those devices listed in Sec. 820.30(a)(2). This regulation does not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance. Manufacturers of human blood and blood components are not subject to this part, but are subject to part 606 of this chapter. ...”

Further, the only time Part 820 is directly mentioned is one time in the Glossary, “CAPA – ‘Corrective and preventive action’: A systematic approach which includes actions needed to: correct (‘correction’); prevent recurrence (‘corrective action’); and eliminate the cause of potential (‘preventive action’) nonconforming product and other quality problems. [21CFR 820.100]”

Thus, this reviewer finds that the commenter’s statement is at odds with reality and should, therefore, be disregarded.

“Section II B – Lines 92-94 (clarify). One of FDA's stated reasons for this guidance is to ‘harmonize the cGMPs (sic)...and FDA’s own medical device quality system regulations.’ The guidance format is not an appropriate means of harmonizing regulations or revising regulations. We ask FDA to comment on this stated purpose and how it is consistent with the statement in lines 24-25 that this guidance ‘is not intended to place new expectations on manufacturers.’”

Because this commenter:

- Left out the contextual introductory statement, “In addition to being part of the FDA's CGMP initiative, this guidance is being issued for a number of reasons.”
- Conveniently, misquotes and elides the text passage quoted (“It is important that we harmonize the CGMPs to the extent possible with other widely used quality management systems including ISO 9000, non-U.S. pharmaceutical quality management requirements, and FDA’s own medical device quality system regulations. With the globalization of pharmaceutical manufacturing and the increasing prevalence of drug- and biologic-device combination products, the convergence of quality management principles across different regions and among various product types is very desirable”) to leave out the key phrase “to the extent possible” and artificially raise the importance of the FDA’s QSR form one of a list of “widely used quality management systems including ...,”

this reviewer finds that the Agency should simply ignore this, *at best*, baseless and unsupported request.

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“Section II B – Line 98 (change/add). To make the guidance more specific, it would be helpful to modify the line as follows: ‘certain types of improvements without the need for a prior regulatory filing. Sufficient process knowledge enables classification of proposed changes into three categories: 1) Those that can be managed within a firm’s quality systems, 2) Those that are appropriately performed under an approved comparability protocol, and 3) Those that require a pre-approval supplement.’”

Because this reviewer finds that the suggested changes do not address the subject of this guidance and would be more appropriately addressed in those FDA venues that address such items, this reviewer suggests that the requested change and addition should not be considered for inclusion in this guidance.

“Section II C - Page: 2

Line 112 (insertion). To emphasize the perspective of management of change lines 125-6 should be moved here.”

Even if, *as this reviewer thinks*, the intended text is lines 123-125, this reviewer does not support moving the text as the commenter suggests.

“Section III – This section is a general overview of the current state of affairs. It is not clear how this provides guidance to Industry.

Since this commenter makes no suggestion that this section of the guidance should be removed and since it provides the linkage between CGMP, the Agency’s current inspection practices, and the quality system model used as the basis for the guidance provided, this reviewer suggests that: **a)** the commenter’s apparently off-the-cuff remarks be ignored and **b)** the commenter should read this section and the constructive comments submitted to the docket about it at least twice more.

“Section III B - Page: 2

Line 166 (add). ‘... products.’ For example, with the production of components such as biologically-derived macromolecules, consideration of comprehensive quality systems and the aspects of quality by design discussed herein are generally recognized as relevant.”

Since the text locations, “Page: 2 Line 166,” do not appear to match the published guidance text and adding the word “products” to the end of the last sentence would make it read, “A quality system provides a sound framework for the transfer of process knowledge from development to the commercial manufacturing processes and for postdevelopment changes and optimization *products*” or perhaps the commenter meant “...commercial manufacturing processes and *products* for postdevelopment ...,” this reviewer leaves it to the Agency to address this comment.

“Section III C – This section could provide more information regarding expectations for risk assessment and management.”

This reviewer respectfully disagrees with the commenter here.

The additional information that is truly required is appropriately provided later in this guidance.

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“Section III E– Lines 196-198 (clarification). FDA addresses ‘...creating a regulatory environment that encourages change towards continuous improvement. This means a manufacturer is empowered to make changes based on the variability of materials used in manufacturing and optimization of the process from learning over time.’ We ask FDA to provide a discussion of the regulatory environment where these changes are possible outside of existing regulations and guidance. It clearly applies to PAT initiatives, but they will likely be limited both in scope and in the number of companies who incorporate them and thus are not broadly applicable. Please address how implementation of ‘continuous improvement’ is encouraged and supported in 21CFR314.70 and in existing FDA guidances on post approval changes. Is industry to consider that this regulation and existing guidance (SUPACs and other) will be substantially revised?”

As far as this reviewer can see, the guidance goes as far as it should because the areas of the commenter’s request are outside the scope of this guidance.

The commenter’s request here should simply be ignored or addressed in other venues.

“Section III E - Page: 3

Line 199 (add) ‘... make data driven changes’”

Again, this reviewer is opposed to the change suggested for a number of reasons not the least of which are:

- a. Its failure to address the requirements for scientific soundness, QU approval, and, *if required by Agency regulations*, submitted to the Agency – even when representative points are evaluated and the appropriate statistical procedures are employed, changes can only be proposed to the firm’s QU and, if approved by said QU and subject to Agency review, submitted to the Agency.
- b. The fact that there commenter’s “Line 199” is blank in the published draft guidance.

“Section III F – Some tasks are broken out between QA and QC while others are together as a responsibility of the quality unit. It is not clear if FDA is trying to recommend how industry should allocate responsibilities in the Quality Unit. If so, all responsibilities should be allocated. Also, trend analysis can be performed by the QC unit. Does that violate the expectations of the guidance? The Scope of the Guidance section states that this guidance does not create new expectations, but delineating specifics for QA and QC could be interpreted as creating new expectations.”

First of all, in context, it is clear that the Agency is merely reporting what it sees as the typical allocation of responsibilities in the industry.

Second, because this document is guidance, the FDA is not engaged in any of the activities that the commenter finds to be a problem.

Given the preceding, this reviewer suggests that the Agency should simply ignore the commenter’s misplaced remarks.

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“Section IV - Line 291 (add) ‘...regulations.’ The utility of the quality systems model is for the manufacturer, and this guidance does not suggest development of new quality elements or models directly subject to regulatory and inspection coverage.”

Since the text referenced already ends with the word “regulations,” this reviewer again suggests: **a)** the commenter is commenting on a different (probably earlier) version of the guidance and **b)** the Agency should simply ignore this misplaced comment.

“Section IV A - Define ‘Management’ as there are usually multiple layers of management in an organization.”

This reviewer does not agree with the commenter here.

The term “management,” though it is has more than one definition, is well and properly defined in most dictionaries and should not, therefore, be defined in this guidance just as words with common definitions, such as “different” and “provide,” should not be defined.

“Section IV A 1 - It may be helpful to add expectations for training and consequences of non-compliance.”

This reviewer does not agree because the topic of this section of this guidance is **“THE QUALITY SYSTEMS MODEL” – NOT “TRAINING”** and certainly **NOT “NONCOMPLIANCE.”**

Adding tangential and/or off-topic text is not helpful to those who genuinely read a document with the intent of being informed about the topic under discussion.

“Section IV A 1 – Line 327 (clarify). It is not clear how FDA would like management to show ‘strong and visible support.’”

As this reviewer and most in the pharmaceutical industry understand, it is management’s responsibility to determine “how” to do something.

One of the Agency’s responsibilities is simply to provide, when it can and where it sees a general need, guidance to one or more approaches that the FDA *currently* thinks can be used to address some issue of concern to the general public, the industries it regulates, and/or the Agency.

Thus, the commenter’s request here is, at best, misplaced.

“Section IV A 2 – Line 341 (add). Responsibilities and authorities should be documented through job descriptions and organization charts. Structure of the organization should include information on conflicts of interest.”

While this reviewer has no problem supporting the addition the commenter’s first statement, this reviewer leaves it up to the Agency to determine if the commenter’s second statement should be included in this guidance.

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However, if this somewhat tangential statement is to be included in this guidance this reviewer recommends that the commenter's first statement should be generalized to read:

"In this regard, all responsibilities and authorities should be documented (e.g., job descriptions and organization charts)."

"Section IV A 3 – Line 356 (edit). The term 'recommends' should be revised to strengthen the concept that Senior Management is ultimately responsible."

Because this is a guidance document, this reviewer cannot support the commenter's suggestion because such is clearly outside of the scope of guidance, in general.

"Section IV A 3 – Line 367 (edit). The term 'recommended', in practice, is really 'expected.'"

In general, unless citing a specific element that is explicitly required in a quality system, the Agency should, as it does here, use words like "suggest" and "recommend."

Based on this, this reviewer does not support the commenter's recommendation here.

"Section IV A 4 – Line 396 (edit). The term 'recommended' should be replaced with 'expected.'"

The reviewer leaves it up to the Agency to decide whether the suggested change should be made.

"Section IV A 5 – This section provides much more detail on expectations. It would appear that some of these details are options for Industry to consider. For example, on line 420 it may not be appropriate for FDA to suggest agenda items and this not really implied in part 211."

This reviewer does not support the commenter's position because, as guidance, the Agency can suggest what it knows is needed and, *in this case*, the suggestion is properly tempered by the word "typically" and merely reflects the reality observed in firms that have implemented a quality system.

"Section IV B 3 – Line 504 (clarify). It is not clear what a generic quality system model is. It may be best to define the standards versus compare them to the generic quality system models."

If the commenter does not understand what a "generic quality system model is," this reviewer suggest that the commenter should obtain copies of the appropriate ISO 9000 series quality standards and study them.

Moreover, the text in question, "Note that the CGMP regulations require a higher standard for calibration and maintenance than most generic quality system models," is simply making a statement of fact.

Based on the preceding, this reviewer recommends that the Agency simply ignore this comment.

"Section IV B 4 – Line 518 (add) '...qualified through an on site audit.'"

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Since the text referenced in Line 518 states, "Under a quality system, the manufacturer ensures that the contract firm is qualified," it accurately reflects the general requirement/expectation of quality systems but does not limit the means of its accomplishment and the addition that the commenter apparently suggests, "through an on site audit," is restrictive and may not be required in every instance, this reviewer can only support the commenter's suggested addition if it is changed to state, "Under a quality system, the product manufacturer ensures that the contract firm is qualified through an on site audit or by other means, as appropriate."

However, cognizant of the possibly applicable remarks in the Preamble to the 1978 CGMP regulations, this reviewer leaves the final decision up to the Agency as to whether to add the reviewer's revised addition, or not.

"Section IV B 4 – Lines 521-522 (clarification). It is unreasonable to expect that senior company officials of a large multi-national pharmaceutical company are '...familiar with the specifics requirements of the contract.' The appropriate management needs to be well informed but this often stops far short of the office of the most senior officers in the organization. Assignment of business responsibilities does not seem to be within the range of application of GMP (sic)."

First of all, generic quality systems standards do assign/focus on management responsibilities.

Second, since this section is presenting guidance here to the quality system model outlined by the Agency, the range of application of CGMP is not relevant here.

Third, the text in question simply states, "It is critical in a quality system to ensure that the contracting manufacturer's officers are familiar with the specifics requirements of the contract."

Since the commenter's problematic phrase seems to be is "ensure that the contracting manufacturer's officers are familiar" and the commenter obviously has a problem with the word "officers," this reviewer recommends revising the text to state:

"It is critical in a quality system to ensure that the responsible senior managers (or officers) for the contracting manufacturer understand the specific requirements of the contract."

which should both address the commenter's concerns and make it clear that a quality system expects that all of the responsible managers (in quality, operations and management) must understand the specific requirements in the contracts to which their firms are a party.

"Section IV C 2 – Line 589 (edit). The term 'should be' is actually an expectation."

Since the commenter recommends no change, this reviewer sees no need to change the text here.

"Section IV C 3 – Line 628 (edit). The term 'recommended' is actually an expectation."

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Since there is no “term ‘recommended’” in Line 628, this reviewer suggests that the Agency ignore the commenter’s apparently misplaced remark.

“Section IV C 4 – Line 660 (add) ‘... continues through process monitoring and trending to ensure that the validated state is maintained after the formal validation exercise.’ This may also provide the basis for change management to effect improvements.

Though this reviewer does not object to adding text that clarifies the statement in question, “Thus, in accordance with the quality systems approach, process validation is not a one time event, but an activity that continues,” this reviewer does object to the commenter’s added statement, “This may also provide the basis for change management to effect improvements” because it detracts from the subject being discussed here.

However, *rather than adding the commenter’s conflicted “... continues through process monitoring and trending to ensure that the validated state is maintained after the formal validation exercise” which ignores the clear each batch, in-process requirement for a manufacturer or processor “... to validate ...” its processes (see 21 C.F.R. 211.110(a))*, this reviewer recommends the simple but effective change to state:

“Thus, in accordance with the quality systems approach, process validation is not a one time event, but an activity that continues for as long as that process is used.”

Hopefully, the commenter and the Agency will see the logic of the reviewer’s remarks and agree to the simple change this reviewer proposes.

“Section IV C 4 – Line 733 (edit). The term ‘recommends’ should be replaced with ‘expects.’ Also, it may not be acceptable to statistically invalidate test results. This concept should be deleted from this guidance.”

Since the comment contains the phrase, “statistically invalidate test results,” it would seem that the commenter is referring to Line 730 since this is the only Line in the draft’s text that contains the word “invalidate.”

However, *if this is the case*, the sentence in question does not contain the word “recommends” or any variant thereof.

Again, this comment seems to be referring to some version of this guidance that is different from the published one.

Therefore, the Agency should disregard this comment.

“Section IV D 2 – Line 819 (add). It is acceptable for a company to refuse an FDA request to copy internal audit reports.”

This reviewer leaves it up to the FDA to address the commenter’s question here.

“Section IV D 3 – Line 837 (add) ‘... manage and control change.’ It is also useful to document the nature of the data upon which the risk assessment was made. This helps to capture process understanding and may help to identify opportunities for improvements.”

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Since that phrase is already in the text referenced by the commenter, the Agency should ignore this comment.

“Definitions – Line 1084 (add) ‘ ...senior management is ultimately responsible for quality.’”

This reviewer leaves addressing this comment to the Agency.

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**EMC-06 Comments By Active Pharmaceutical Ingredients Committee (APIC),  
Posted 10 December 2004**

APIC begins by stating:

**“Introduction.**

CEFIC is the European organization of the chemical industry representing national federations, companies and more than 100 affiliated associations and sector groups, located in Europe. All together CEFIC represents directly or indirectly more than 29,000 large-, medium- and small chemical companies in Europe which employ about 1.7 million people and account for nearly a third of the world chemical production.

APIC is one of CEFIC sector groups, comprising European producers of active pharmaceutical ingredients (APIs) and intermediates. This product range implies that CEFIC/APIC is a major stakeholder regarding new pharmaceutical Regulations and Guidelines, in particular for those that affect APIs and intermediates. We, therefore, take the opportunity for submitting our members' comments on the above-mentioned Draft Guidance.

We have limited our comments hereunder to “General Comments” because of the character of the comments.”

APIC's reviewed comments are as follows:

**“General Comments.**

CEFIC/APIC very much support this document because it is very helpful to modernize and to harmonize quality systems in the pharmaceutical industry.

We are a bit disappointed by the fact that the scope of the document is limited to drug products (finished pharmaceuticals). In our opinion the scope of this document should also include specific reference to the manufacture of Active Pharmaceutical Ingredients (API). The approach of Quality systems is as much applicable for API manufacturers as for drug product manufacturers.

Furthermore in the document reference can then be made to the GMP (sic) requirements for APIs (ICH Q7a).”

Though this reviewer notes that Lines 115-116, “It may also be useful to manufacturers of components used in the manufacture of these products” in the **“II. C. Scope of the Guidance”** do include manufacturers “of Active Pharmaceutical Ingredients (API)” because, *by statute*, components of drugs, *including drug products*, are drugs.

However, this reviewer does not support adding a “specific reference to the manufacture of Active Pharmaceutical Ingredients (API)” because APIs are excluded from the scope of the finished pharmaceutical CGMP (21 C.F.R. Part 211).

On balance, this reviewer defers to the FDA's judgment and supports the current limitations on the guidance's scope.

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**C-14 Comments By Japan Society of Pharmaceutical Machinery and Engineering  
(JSPME), Posted 15 December 2004**

**SEE: EMC-03 Comments By Japan Society of Pharmaceutical Machinery  
and Engineering (JSPME), Posted 10 December 2004, because this  
posting is a duplicate of that submission.**

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**C-15 Comments By European Federation of Pharmaceutical Industries and  
Associations (EFPIA), Posted 15 December 2004**

EFPIA begins by stating:

“Please find enclosed EFPIA comments with respect to the above-mentioned document. We thank the FDA for providing us with the opportunity to comment on this document ...”

EFPIA's reviewed comments are as follows:

**General comments**

EFPIA wishes to congratulate the FDA in maintaining momentum with its Science and Risk based initiatives for Pharmaceutical Development and Manufacturing, including the issue of this guidance which represents an important milestone and update in the thinking of the FDA and its philosophy towards pharmaceutical development and manufacturing. It is welcomed that FDA recognises that cGMP (sic) regulations do not consider all of the elements that today constitute most quality management systems.”

In general, except for the less than appropriate use of the acronym “cGMP (sic)” when the correct acronym is “CGMP,” which is the acronym used more than 90 times in this guidance, this reviewer agrees with the commenter's last statement and accepts that the first two sentences are the commenter's opinion.

“EFPIA is fully supportive of the intent of this document. EFPIA is very supportive of the need to modernise and to harmonize pharmaceutical Quality Systems and regulatory processes to enable a culture of Quality improvement, whilst building in some potential for regulatory flexibility for the filing of changes and inspectional coverage for companies showing good product and process knowledge and good quality systems.”

No where in the draft guidance does this reviewer finds statements that support the commenter's “building in some potential for regulatory flexibility for the filing of changes and inspectional coverage for companies showing good product and process knowledge and good quality systems” and, especially with respect to inspectional flexibility, this reviewer reminds both the commenter and the Agency that there is a statutory “not less than every two years” general inspection requirement for every drug facility that limits the Agency's legal latitude in that regard.

“We believe this guidance provides industry a significant additional impetus to change its manufacturing and quality process philosophy from a reactive post-manufacturing quality testing regimen into one directed towards a manufacturing operation focussing on proactive control and based on science and technology, with quality designed into the process and the product in order to achieve business process excellence.”

This reviewer finds that the commenter's “reactive post-manufacturing quality testing regimen” remark about the CGMP regulations for finished pharmaceutical are somewhat misleading because, today, the CGMP regulations clearly require the establishing, monitoring and validating of each batch of product during its production and the use of statistical process control to achieve that end (21 C.F.R. Sec. 211.110) and allows the manufacturer or processor to achieve these

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goals by any scientifically sound and appropriate means – so, though they seem not have been doing so, firms could have been “building quality in” since 1978 but consciously chose not to do so.

As evidence of the validity of the reviewer’s remarks, the reviewer offers the factual reality that most of today’s firms do not rigorously control all of the critical characteristics of the components they use in the manufacturing of their drug products – usually using the lame justification that these manufacturers and processors must buy components with whatever variability that is generally offered for sale.

“We would urge the FDA to include within the scope of the quality systems some additional aspects such as:

- Information Management Systems. Information management is the key to most of our business processes and the need to manage data, knowledge and experience gathered has become an essential element. The requirements for computer system validation do not encompass the concept of managing business processes and managing information.
- Corporate Quality Systems. For globally operating companies, the global and local quality systems need to be harmonised. This aspect is often mentioned during FDA inspections and it would be useful to make a reference to the scope of corporate and local quality systems.”

Though the commenter’s first bullet accurately portrays the commenter’s understanding of the explicit requirements of 21 CFR Parts 210 and 211 and 21 CFR Part 10, this reviewer notes that nothing in said regulations prevent a manufacturer from addressing “the concept of managing business processes and managing information” in the systems they adopt.

With respect to the commenter’s second bullet, this reviewer again notes that there is nothing in the current FDA regulatory environment that precludes a firm from “harmonizing” their global and local quality systems provided those firms regulated by the FDA do so in a manner that complies with all aspects of CGMP (statutory and regulatory) – something that many firms do not seem to be doing in this reviewer’s experience.

In one or more key areas, including, but not limited to, incoming, in-process, and drug product control, many drug product manufacturers, processors, and packers seem to be knowingly operation in a manner that does not meet the applicable clear minimums established in 21 CFR Part 211.

Hopefully, the Agency and the commenter will review and accept the reality of the preceding remarks.

**“Specific comments**

Inspection Scope (reference line 290,304 - 335,390 - 393)

It is welcomed that this document gives guidance on how the implementation of comprehensive quality systems can help manufacturers achieve compliance, but does NOT create new expectations for pharmaceutical manufacturers that go beyond the requirements laid down in

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current regulations. Although industry welcomes a quality systems approach to inspections, some of the guidance given in this document, for example:

- the expectations for management, (lines 304 - 334)
- the requirement to use “a formal quality planning process” and “measurable goals that are monitored regularly ” (line 390 - 393)

although sound and valid, go beyond the current regulations.

This reviewer sees that the commenter has apparently mischaracterized this guidance's scope, intent and advice concerning the quality systems approach to the pharmaceutical current good manufacturing practice regulations set forth in 21 C.F.R. Parts 210 and 211 as well as the reach of the underlying key statutory provision (21 U.S.C. Sec. 351(a)(2)(b)) upon which the CGMP regulations rest.

Factually, the Federal Food, Drug, and Cosmetic Act as amended, commonly abbreviated as the “FDC Act,” in 21 U.S.C. Sec. 351(a)(2)(B), states:

“Sec. 351. Adulterated drugs and devices

A drug or device shall be deemed to be adulterated--

(a) Poisonous, insanitary, etc., ingredients; adequate controls in manufacture

(2) ... (B) if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this chapter as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess;

Thus, *though the CGMP regulations set forth in 21 C.F.R. Parts 210 and 211 establish a floor below which it is obvious that a non-complying drug is adulterated, the FDC Act establishes another hurdle* that a manufacturer, processor, packer or holder (as well as, based on 21 C.F.R. Sec. 210.3(b)(12), packager of, labeler of, tester of, and quality controller of drug products) **must meet** for a drug or drug product – such firms must have facilities and controls, and use methods that provably conform to, operate and be administered in conformity with **current good manufacturing practice** (CGMP).

In an era where firms in most other industries are increasingly being operated under some quality system or quality management system, it therefore becomes increasingly difficult for a pharmaceutical firm not to be operated in compliance with a quality system and still claim to comply with the strictures established in 21 U.S.C. 351(a)(2)(B).

The FDA, recognizing this reality, has therefore moved to advise the industry, through this guidance, about one regulation-compliant approach whereby a firm can ensure that it becomes statutorily compliant with CGMP since it is, or should be, obvious to this commenter and others that having a quality system has become or, at the least, is rapidly becoming an integral part of “**current good manufacturing practice**” in the United States of America.

Given the preceding factual realities, this reviewer finds that the commenter's “some of the guidance given in this document, ..., although sound and valid, go beyond the current regulations” is apparently knowingly (as word, “knowingly” is defined in 21 U.S.C. Sec. 321(bb)(1)) misleading.

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Moreover, this reviewer does not share this commenter's hopefully feigned concern because, *as any person trained in the CGMP that is applicable to his or her assigned tasks (as this firm's assigned commenters are required to be)*, FDA investigators should know which are regulatory requirements, which are not such requirements, and which fall within the scope of other regulations or the statutory scope of 21 U.S.C. 351(a)(2)(B).

Further, *as any knowledgeable compliance person, including the FDA's trained drug "investigators," should*, this reviewer understands:

- The Quality System "expectations" explicitly set forth in this guidance as "expectations" fall outside of the CGMP "regulations"
- These Quality System "expectations" *probably* are within the statutory scope of CGMP as set forth in 21 U.S.C. Sec. 351(a)(2)(B) because these are generally recognized by today's industries as clear Quality System requirements, and
- All valid Quality System "expectations" *definitely* are within the statutory scope of CGMP as set forth in 21 U.S.C. Sec. 351(a)(2)(B) when a firm formally implements **any** quality system including one based on the Quality System Model set forth in this guidance.

Based on all of the preceding, the Agency should ignore the commenter's obviously "naive" understanding of the scope CGMP.

"Care needs to be taken that this guidance does not raise the expectations of inspectors or lead to the citation of deviations related to this guidance as opposed to deviations related to compliance with the cGMP (sic) regulations."

This reviewer does not share this commenter's concerns and notes that the commenter's remarks are, at best, misplaced and seemingly denigrate the competence of the Agency's inspectors.

There are also several examples of cGMP (sic) requirements being compounded in sentences with non-cGMP requirements. Some examples are lines 518-521, lines 674-683, lines 543 - 547. Clear communications are needed to position this guidance with the status of the cGMP regulations.

Having read the passages in question in their context, this reviewer would again refer the commenter and the Agency to this reviewer's comments on statutory CGMP as set forth in 21 U.S.C. Sec. 351(a)(2)(B).

It is stated (line 290) that FDA will only inspect against CFR requirements. This is necessary.

This reviewer finds that the commenter apparently does not understand American English.

Factually, the sentence in question states, "FDA regulatory and inspectional coverage will remain focused on the specific CGMP regulations."

Thus, it is apparent that the commenter has confused the guidance's "focused on" with "limited to."

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Thus, this reviewer would recommend that the commenter reread the sentence in question and that the Agency ignore this misplaced comment.

“However, it would be desirable to clarify that inspections should be conducted using the document entitled ‘Risk based method for prioritizing cGMP inspections of pharmaceutical manufacturing sites’, published by the FDA in September 2004.”

Since:

- This guidance presents a “Quality Systems” approach to “Pharmaceutical CGMP” and in not a guidance on “inspections,” and
- The document referenced by the commenter is simply a method that is subject to change,

this reviewer knows that this comment should simply be ignored.

“This will not only facilitate the inspection but will also be the start of a consistent global approach, moving the industry and the regulators from a compliance mentally to a science and risk based quality systems model.”

This reviewer does not agree with the commenter here because the comment ignores the reality that the CGMP regulations are risk-based as all statistics-based approaches to control are and speaks to “a science and risk based quality systems model” when, *by definition*, quality systems models are factually control-based.

Thus, *at best*, the use of the phrase “science and risk based” is an inappropriate adjective modifier for any “quality systems model.”

In addition, *since all controls are required, under CGMP (21 CFR 211.160(a), to be scientifically sound and appropriate*, and the CGMP regulations spell out the risk-based *minimums* for incoming materials, in-process materials, labeling and the finished drug product and 21 U.S.C. Sec 360(h),

“Every establishment in any State registered with the Secretary pursuant to this section shall be subject to inspection pursuant to section 374 of this title and every such establishment engaged in the manufacture, propagation, compounding, or processing of a drug or drugs or of a device or devices classified in class II or III shall be so inspected by one or more officers or employees duly designated by the Secretary at least once in the two-year period beginning with the date of registration of such establishment pursuant to this section and at least once in every successive two-year period thereafter.”, clearly spells out the legal minimum inspection interval, and 21 U.S.C. Sec. 374, “Inspection.

(a) Right of agents to enter; scope of inspection; notice; promptness; exclusions

(1) For purposes of enforcement of this chapter, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs or restricted devices are manufactured, processed, packed, or held, the inspection

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shall extend to all things therein (including records, files, papers, processes, controls, and facilities) bearing on whether prescription drugs or restricted devices which are adulterated or misbranded within the meaning of this chapter, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this chapter, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this chapter. No inspection authorized by the preceding sentence or by paragraph (3) shall extend to financial data, sales data other than shipment data, pricing data, personnel data (other than data as to qualification of technical and professional personnel performing functions subject to this chapter), and research data (other than data relating to new drugs, antibiotic drugs, and devices and subject to reporting and inspection under regulations lawfully issued pursuant to section 355(i) or (k), section 357(d) or (g), section 360i, or 360j(g) of this title, and data relating to other drugs or devices which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 355(j) of this title). A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

(2) The provisions of the second sentence of paragraph (1) shall not apply to--

(A) pharmacies which maintain establishments in conformance with any applicable local laws regulating the practice of pharmacy and medicine and which are regularly engaged in dispensing prescription drugs or devices, upon prescriptions of practitioners licensed to administer such drugs or devices to patients under the care of such practitioners in the course of their professional practice, and which do not, either through a subsidiary or otherwise, manufacture, prepare, propagate, compound, or process drugs or devices for sale other than in the regular course of their business of dispensing or selling drugs or devices at retail;

(B) practitioners licensed by law to prescribe or administer drugs, or prescribe or use devices, as the case may be, and who manufacture, prepare, propagate, compound, or process drugs, or manufacture or process devices, solely for use in the course of their professional practice;

(C) persons who manufacture, prepare, propagate, compound, or process drugs or manufacture or process devices, solely for use in research, teaching, or chemical analysis and not for sale;

(D) such other classes of persons as the Secretary may by regulation exempt from the application of this section upon a finding that inspection as applied to such classes of persons in accordance with this section is not necessary for the protection of the public health.

(3) An officer or employee making an inspection under paragraph (1) for purposes of enforcing the requirements of section 350a of this title applicable to infant formulas shall be permitted, at all reasonable times, to have access to and to copy and verify any records--

(A) bearing on whether the infant formula manufactured or held in the facility inspected meets the requirements of section 350a of this title, or

(B) required to be maintained under section 350a of this title.

(b) Written report to owner; copy to Secretary

Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary.

(c) Receipt for samples taken

If the officer or employee making any such inspection of a factory, warehouse, or other establishment has obtained any sample in the course of the inspection, upon completion of the inspection and prior to

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leaving the premises he shall give to the owner, operator, or agent in charge a receipt describing the samples obtained.

(d) Analysis of samples furnished owner

Whenever in the course of any such inspection of a factory or other establishment where food is manufactured, processed, or packed, the officer or employee making the inspection obtains a sample of any such food, and an analysis is made of such sample for the purpose of ascertaining whether such food consists in whole or in part of any filthy, putrid, or decomposed substance, or is otherwise unfit for food, a copy of the results of such analysis shall be furnished promptly to the owner, operator, or agent in charge.

(e) Accessibility of records

Every person required under section 360i or 360j(g) of this title to maintain records and every person who is in charge or custody of such records shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to, and to copy and verify, such records.”

spells out the legal minimum inspection scope for each such inspection, it would seem that the “inspection method” document that the commenter references clearly violates the minimums established in the Food, Drug, and Cosmetic Act (FDC Act) and, considering the unanimous 1988 Supreme Court decision of 1988 (*Berkovitz v. US*) and the preamble of the Generic Drug Enforcement Act, those responsible for issuing that document may have knowingly subverted the regulatory process and may be subject to criminal prosecution and debarment for issuing a document that is clearly at odds with the legal minimums set forth in the cited sections of the FDC Act.

Given the preceding, this reviewer recommends that this guidance continue, as it has done, to acidulously avoid changing the text in the manner suggested by this commenter.

“EFPIA recommends that references to cGMP (sic) regulations be deleted and that it is clearly stated that the paper is only intended to be guidance for a model quality system. This will facilitate the use of the guide for both drug products and drug substances and will also facilitate its use as a model for an internationally harmonized quality system guide.”

The commenter’s obviously illogical recommendation should be ignored.

First, contrary to the commenter’s position that this document “is only intended to be guidance for a model quality system,” the guidance is clearly, *as it should and its title plainly states*, a “**Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations.**”

Since this guidance plainly addresses the a quality systems approach to pharmaceutical current good manufacturing practice (CGMP), the commenter’s suggestion “that references to cGMP (sic) regulations be deleted” is obviously unsupportable.

Moreover, from the title and the text it is, *or should be*, obvious that this document is not a “guidance for a model quality system.”

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**Implementation of Regulatory Flexibility** (reference lines 98 - 103)

“The principles outlined in lines 98- 103 are fully supported. Further clarity will need to be developed on the mechanisms as to how Industry and FDA will work together to define and apply ‘regulatory flexibility’ for filings and inspections where a company meets the criteria for good process knowledge and good quality systems.”

While the commenter’s request is artfully constructed, it overlooks the reality that US statutes and binding FDA regulations establish the limits on the allowable “regulatory flexibility” and not the quality system or how it is implemented.

In addition, since there are FDA documents that directly address changes and the rules governing them, the commenter should address its requests and suggestions to these documents and not to this guidance.

Based on the preceding realities, the Agency should ignore this request because it is not germane to the guidance issues being addressed.

**“Scope of the document** (reference line 116)

The scope of the document should also include specific reference to Drug Substance (API) manufacture, as it is not clear if this is included. Many companies operate one quality system for all their manufacturing sites, whether they are for drug substance or drug product manufacture and the Quality System approach is equally applicable to drug substance and drug product manufacturers.

Though this reviewer notes that Lines 115-116, “It may also be useful to manufacturers of components used in the manufacture of these products” in the “**II. C. Scope of the Guidance**” do include manufacturers “of Active Pharmaceutical Ingredients (API)” because, *by statute*, components of drugs, *including drug products*, are drugs.

However, this reviewer does not support adding a “specific reference to the manufacture of Active Pharmaceutical Ingredients (API)” because APIs are excluded from the scope of the finished pharmaceutical CGMP (21 C.F.R. Part 211).

Further, because there is no detailed CGMP Part for bulk drugs or active pharmaceutical ingredients that would apply to ‘Active Pharmaceutical Ingredients’ (APIs), the Agency appropriately limits this guidance’s scope to drug products.

On balance, this reviewer defers to the FDA’s judgment and supports the current limitations on the guidance’s scope.

If APIs are included in the scope, components should not be mentioned (line 116) as this raises expectations beyond current requirements.”

Since this is a guidance document and the sentence in question simply states, “It may also be useful to manufacturers of components used in the manufacture of these products” in the “**II. C. Scope of the Guidance**,” the optional nature of the text (“it may also be useful” clearly raises no expectations – as it merely presents an option that may or may not be adopted.

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Since neither the word “should” nor the phrase, “is expected” are used, there can be no “expectations” and, *since this is a guidance document*, no “requirements” are stated or implied.

On balance, this reviewer defers to the FDA’s judgment and supports the current text.

**“References to GMP**

The specific references to selected parts of the cGMPs (sic) seen in a number of areas in the document should be removed from the guidance to avoid potential confusion.”

The commenter’s misguided remarks here should be disregarded.

“In addition, as this document should be equally applicable to APIs as to drug products, if the cGMP (sic) references are kept, they should also include the’ references to the GMP guidance for APIs (Q7A).”

Factually, the commenter is incorrect because, to those who study and understand the drug and the finished pharmaceutical (drug Product) CGMP understand, there is no API CGMP Part in Title 21 of the C.F.R., and, this, this document is clearly NOT equally applicable to APIs as it is to drug products because there is no API CGMP – there is only a drug product CGMP.

Further because this document is an approach to “Pharmaceutical CGMP” guidance and not an approach to GMP for APIs, it is only appropriate to include references to the Pharmaceutical CGMP.

Furthermore, the “GMP guidance for APIs (Q7A)” clearly conflicts with the legally binding minimums of the drug product CGMP,

For all of the preceding reasons, this reviewer knows that this commenter’s remarks here should be ignored by the Agency.

“An alternative mechanism rather than this guidance could be Q&As on the FDA website, which could be used to address specific cGMP (sic) interpretations (e.g. lines 613-619 on alternative approaches to assuring the reliability of suppliers).”

This reviewer finds the commenter’s suggestion problematic because it incorrectly suggests that the key issue is the interpretations of specific CGMP requirements when, in reality, the CGMP regulations in question establish clear minimums that need no such interpretation – plainly, the regulated firm must comply with the stated CGMP minimums and failing to do so renders each batch so produced adulterated.

Thus, this reviewer again recommends that the Agency ignore this commenter’s remarks here and proceed to appropriately revise and issue this obviously helpful guidance.

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**“Definition of Achieving Quality** (reference Line 154)

Achieving Quality is defined in the document as ‘achieving identity, strength, purity, and other quality characteristics designed to assure the required levels of safety and effectiveness’. This is a narrow definition which could be further improved to be more in line with the tone of the guidance.”

First of all, this reviewer notes that, in context, the text in question actually states:

**“A. Quality**

Every pharmaceutical product has established identity, strength, purity, and other quality characteristics designed to ensure the required levels of safety and effectiveness. For the purposes of this draft guidance document, the phrase *achieving quality* means achieving these characteristics for the product.”

This reviewer finds that this commenter’s “narrow definition” remark seem to be, at best, a not so subtle attempt to distort the requirements of both a *quality-oriented quality management system* and the current CGMP regulations.

Factually, *even when a truly robust quality system is in place*, the manufacture of large collections (batches or lots) of product units still requires that appropriate statistical testing be done on an appropriate number of representative units having variable characteristics that must be ensured of being met. [Note: In that regard, the number required for batches drug units of the size typically produced could validly be reduced from the need to test 200, or more, such representative drug-product units to the need to test only 40-some-odd units for each critical variable characteristic and the number of critical variable characteristics reduced from the current typical number of four (4) [typically, taken from the applicable uniformity characteristics such weight, content, drug release, impurity level, water content, deliverable volume, particulates, and preservative level and assay and sterility] to, in the most favorable cases only one (1) or, at most, two (2) critical variables.]

Moreover, the definition presented is clearly in line with the text of the guidance and the basis, CGMP, on which the regulation of drugs stands.

In this reviewer’s understanding, the “tone of the guidance” is a quality system that is based on building in quality to meet the clear minimums so plainly set forth in the drug-product CGMP regulations and, based on this reality, the commenter is mistaken and the commenter’s factually unsupported request should be ignored.

However, this reviewer does support making the definition in question clearer so that those reading this text will clearly understand the minimum expectations for quality under CGMP.

To that end, this reviewer offers the following alternative text:

**“A. Quality**

Every pharmaceutical product has established identity, strength, purity, and other quality characteristics designed to ensure the required levels of safety and effectiveness. For the purposes of this draft guidance document, the phrase *achieving quality* means achieving these characteristics for **all the product units from the time the units are released until after the units have passed their expiration date.**”

Hopefully, after reading this reviewer’s remarks, the commenter better understands the clear minimums that are required for achieving quality in a

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CGMP-compliant manner and either accept the text as proposed or, failing that, offer specific CGMP-compliant alternative text that addresses the commenter’s concern in this instance.

“There is such synergy between the concepts of process understanding, manufacturing science, and quality by design that to limit quality in this manner is to equate quality with meeting specifications.”

This commenter begins with a false premise, “equate quality with meeting specifications,” when what must be achieved is “building quality into the process and product so that the evaluation of a minimum *representative* number of units for their *critical characteristics* ensures that the desired level of quality is consistently achieved for the *untested* units in each batch” – a goal that obviously transcends the commenter’s simplistic “meeting expectations” view.

Further, *without some evaluation*, there is no way that a firm can assess whether or not the desired levels of quality have been met – a reality that the commenter seems to treat dismissively.

Finally, though the commenter uses the words, “process understanding, manufacturing science, and quality by design,” this reviewer finds that many of the firms the commenter represents do not seem to understand what each of these entails much less routinely use these in the manufacture, processing, and packing of the drug products they produce.

That this is true, is clearly reflected in, among other things:

- The failure of those firms to rigorously control the specifications for all of the critical characteristics of each of their incoming components,
- Their ongoing assessment of the formulation of their drug products as an “art,”
- Their ongoing knowing failure to take and evaluate samples (for their critical variable characteristics) that are representative of the lot or batch at each stage of the process as the risk-based CGMP regulations appertaining thereto clearly require, and
- Their continued attempts to justify the less than scientifically sound and appropriate evaluations that they do perform.

Based on all of the above, this reviewer recommends that the Agency disregard the commenter’s remarks here.

“This is part of moving from a compliance mentality to a quality systems approach including science driven basis for determining quality. A better definition of quality and achieving quality would incorporate these concepts.”

Based on the preceding practice realities and the clear requirement minimums of CGMP, the Agency should disregard the commenter’s interesting, but empty and unsupported, rhetoric here.

**“Innovation, Process Improvement and Optimisation** (reference lines 175-183 and 195)

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In section III. "CGMPS and the concepts of modern quality systems", it is felt that the element of process improvement and optimisation is missing. Section D Lines 175 to 183 deals with CAPA, but as pointed out in the white paper on Innovation and Continuous Improvement, a modern quality system needs to look at improvement and optimisation before problems arise. The concept of improvement and optimization therefore needs to be addressed. In addition the concept of innovation needs to be addressed, particularly as the need for innovation is a driving force behind the FDA's initiative."

First, this reviewer notes that, since the topic "optimisation" is one aspect of subject "process improvement," this reviewer accepts the commenter's unusual sentence construction, "element of process improvement and optimisation is missing" instead of "elements of ... are ..."

Second, the commenter's next statement indicates that the commenter's either does not understand "CAPA" at all or views it as "CAPA."

Since "improvement and optimisation" are but aspects of any quality-proactive quality system's CAPA program, this reviewer sees no need to discuss this "element" separately.

Further, since: **a)** "innovation" is but one way that an organization's CAPA system can improve ones processes and products, **b)** "innovation" *per se* does not ensure improvement in quality, and **c)** "*the increasing use of a quality systems approach in a CGMP environment,*" and not "innovation," is the obvious driving force in this guidance, the commenter's unhelpful suggestions here should be disregarded.

However, a section on "Systems Controls" is needed and has been included by this reviewer because this is not only a CGMP minimum but also a quality system expectation.

**"Distinction between QA and QC** (reference lines 207 -212)

The distinction which is now made between QC and QA is welcomed. This distinction brings cGMP (sic) into line with GMP requirements in other regions and also recognises that this is the way in which most pharmaceutical companies are organised."

This reviewer does not agree with the commenter that the text in question addresses a "distinction ... between QC and QA"

Factually, the draft simply:

- Presents the Agency's view of how the responsibilities and authorities of the subunits that comprise today's CGMP-regulated organization's "quality control unit" are typically divided and
- Uses the broader term, "quality unit" as a guidance substitute for the clearly defined CGMP term "quality control unit."

However, this reviewer finds that many firms have a tripartite division of the "quality control unit" into QA, QC and a third unit, typically called Regulatory Affairs (RA), in which many firms invest a portion of the clear CGMP responsibilities and authorities of the "quality control unit." [Note: In some firms, a Vice President of

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Quality ... and Regulatory affairs is the title given to the person assigned as the head the "quality control unit."

Hopefully, the Agency will recognize this reality and appropriately modify this portion of the text.

**"Broadening the Concept from Change Control to Change Management** (Reference lines 185 and 708)

It is recommended that the term Change Management is used instead of Change Control. Change Management is more encompassing than change control and is more consistent with the quality management approach."

While this reviewer would agree that "Change Management" is a different term than "Change Control" and that it is "more consistent with the quality management approach," this reviewer notes that the approach in this guidance "Quality Systems Approach" is not the same as the "quality management approach" alluded to by this commenter.

On this basis alone, the commenter's proposal should be rejected because it is obvious that the commenter either does not understand the difference or, more darkly, is knowingly confusing the two approaches.

"Change Control is still reminiscent of a quality control unit which reviews and dispositions change requests. Change Management is considered to be more comprehensive including not only changes to procedures but changes to equipment, specifications, etc."

Since, by law, the regulated form's "quality control unit" does make the final decision on all change proposals, "including not only changes to procedures but changes to equipment, specifications, etc.," the commenter's rationale is obviously baseless and this obviously anti-CGMP suggestion should be ignored.

"Change Management is more conducive to enabling change to be made in a risk based manner taking into account the integral nature of pharmaceutical systems. Change Management also conveys the concept that change is desirable albeit in a managed process as opposed to change is something that is bad and must be controlled."

This reviewer finds that the commenter's remarks are not only ill conceived but again ignore the clear CGMP minimums set forth in 21 C.F.R. Sec. 211.160(a), "The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified." that plainly recognizes that "specifications, standards, sampling plans," and "test procedures" are controls and require prior review approval by the "quality control unit."

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It is the commenter and not the word "control" that is attempting to impute negatives to the concept of control.

Factually, "control" is a proactive view in a quality systems approach to quality and one that helps ensure the desired level of quality has been achieved.

"Management" is, at best, a quality neutral view in a quality systems approach to quality that carries with it the connotation of putting up with the current lack of control or, worse, using risk-based approaches that are fundamentally anti-quality.

In general, *under CAPA*, the need for changes in an existing process and product is a sign of weaknesses in the underlying process or product and a failure to build quality into that process or product.

On these bases, the commenter's ill-conceived remarks should be ignored.

**"Invalidation of Test Results** (reference line 730)

The word 'statistically' should be deleted from the statement 'invalidation of test results should be scientifically and statistically sound and justified'.

FDA has previously not required statistics be used to invalidate a test result. This requirement is therefore inconsistent with other draft guidances and should not be included in this guidance."

This reviewer agrees with the commenter that the word "statistically" should be deleted along with the word "and" that follows it.

The commenter's rationale proverbially "strains at the gnat and swallows the camel."

Factually, since the term scientifically sound encompasses all proper uses of statistics, the phrase, "scientifically and statistically sound," is an illogical and grammatically incorrect construction

However, this reviewer finds that other changes are also needed and suggests that the sentence containing this text be changed to read:

"Invalidation of test results should be: **a)** scientifically sound, **b)** based on an analyst error, method weakness, or equipment failure established from the critical evaluation (investigation) of all data, and **c)** justified.

The changes suggested by this reviewer reflect the reality that, in a robust CGMP-compliant quality system, conclusive proof of a cause must be found before test results can be unequivocally "invalidated."

**"Auditing** (reference line 808)

On line 808 there is a requirement to audit the entire system at least annually. It is felt that a risk based approach to audits should be taken, with those areas and systems having a higher risk being audited more frequently and low risk areas being audited less frequently. These are the same principles to those outlined in the FDA's new policy for risk-based inspections.

This reviewer cannot support the commenter's suggestion.

This is the case because that suggestion violates one of the fundamental auditing tenets of quality systems and is, therefore, anti-quality.

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Furthermore, unless a firm is able to audit its entire quality system on an ongoing basis so that, at least annually, all of its operational units have been audited, that firm does not truly have a valid quality system for that firm and it cannot validly assess a system it has implemented.

This does not mean that once a year the firm should stop and audit everything – a full audit can be achieved by auditing defined portions of the firm’s operational activities in, for example, the first 11 months of a year and reserving the last month for a review of and report on the global quality system for that firm.

With respect to the commenter’s plaintive, “a risk based approach to audits should be taken, with those areas and systems having a higher risk being audited more frequently and low risk areas being audited less frequently,” there is nothing in this guidance that prevents a firm from auditing some areas at higher frequency as the commenter’s remarks imply – all the guidance does do is suggest a minimum frequency of annually for the overall system as a whole.

With respect to the commenter’s last remark, “These are the same principles to those outlined in the FDA’s new policy for risk-based inspections,” this reviewer can only note that, to the extent that said policy is at odds with the clear language (“at least once in the two-year period beginning with the date of registration of such establishment pursuant to this section and at least once in every successive two-year period thereafter”) contained in 21 U.S.C. Sec 360(h)] and the clear inspection expectation requirements set forth in 21 U.S.C. Sec. 374, which set the applicable statutory minimum inspection requirements for the Agency, the Agency’s policy is patently illegal and should subject those senior governmental officials who are accountable for approving it to the appropriate penalties set forth in the applicable laws.

Given the preceding, the commenter would be well advised to distance itself from this policy rather than cite it as a supportive example.

**“References to ongoing activities**

We suggest that references to other ‘ongoing’ activities (e.g. footnotes 4,5,6.) are removed, or added as true references.”

Since these references are to documents under development, this reviewer support the commenter’s removal suggestion because, in general, a guidance should not refer to documents that are under development.

Further, because the documents in question have not been finalized, it is inappropriate to add such as “true references,” which, *as they only exist in draft form*, they simply cannot be.

*Formal Review Of Comments Submitted To The FDA's Draft Guidance  
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**EC-03 Comments By Compressed Gas Association, Posted 15 December 2004**

The Compressed Gas Association begins by stating:

**"REQUEST FOR 90-DAY EXTENSION OF COMMENT PERIOD "**

Since the commenter makes no comment to the docket, this reviewer did not review the contents of the commenter's request for an extension.

However, this reviewer did address how the e-form, used for submitting electronic comments, could be modified to facilitate the proper classification of such e-submissions as "EEXT" that they are instead of an "EC" which they are not.

*Formal Review Of Comments Submitted To The FDA's Draft Guidance  
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**EC-04 Comments By Pfizer, Posted 15 December 2004**

**SEE: C-02 Comments By Pfizer, Inc., Posted 30 November 2004**, because this posting seems to be a duplicate of that submission.

*Formal Review Of Comments Submitted To The FDA's Draft Guidance  
For Agency & Public Review*

**EC-05 Comments By Alcon, Inc., Posted 15 December 2004**

Alcon begins by stating:

"Provided herewith are two (2) copies of Alcon's comments regarding FDA's Draft Guidance on 'Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations."

Alcon's reviewed comments are as follows:

"Page 13 (line 474) - Further definition of 'continued training' would be helpful. Interpretation of the term "continued training" could lead one to understand that training on every procedure every month / year (?) would be a requirement."

Since the sentence in question simply states, "Under a quality system, continued training is critical to ensure that the employees remain proficient in their operational functions and in their understanding of CGMP regulations," and this is a guidance document, it cannot be interpreted as a "requirement" as the commenter is suggesting.

However, to better align the guidance with the expectations of the CGMP regulations for finished pharmaceuticals vis-à-vis training in CGMP (see 21 C.F.R. Sec 211.25(a) (**bolding** added for clarity), "...**Training** in current good manufacturing practice **shall be conducted** by qualified individuals **on a continuing basis** and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them"), this reviewer suggests changing "continued" to "**continuing**."

In conjunction with this statement, Line 489 - 490 notes "It is important that supervisory managers ensure that skills gained from training be incorporated into day-to-day performance." This might lead one to understand that daily audits on training effectiveness / job performance would be required."

Since the sentence in question simply states a factual observation concerning what is important and this is a guidance document, it cannot be interpreted as a "requirement" as the commenter is suggesting.

Thus, it is up to each firm implementing a CGMP-compliant quality system to have policies, procedures, work instructions and, if needed, other documents that define the firm's practices with respect to the requisite nature, scope, and frequency of actions required to ensure that a firm operating under a CGMP-compliant quality system has proven measures that continually establish "training effectiveness / job performance."

" Page 15 (line 577) 'Distinct labels with discriminating features for different products, ...marketed with different strengths, should be included to prevent mislabeling and ....' The Falcon products within a product line or type (i.e. Levobunolol, Timolol Maleate, Betaxolol HCL) are not distinctively different. See below."

Since the packaging and labels mentioned are not shown in the comment, this reviewer must leave it up to the Agency to review the commenter's remarks here.

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“On page 18 (line 677) the statement ‘Process steps should be verified using a validated computer system or a second person.’ piqued our interest. For example, It would appear that for some processing steps (compounding validated recipes, etc.) we could eliminate the second signature.”

Since the guidance in question does not suggest any elimination of a second signature but rather suggests that a validated computer system’s recorded verification of the completion of a process step could be used as an alternative second signature for the written signature of a second person or its validated secure electronic equivalent, there is no suggestion that the commenter’s firm “could eliminate the second signature” as the commenter asserts.

Thus, the Agency should ignore the commenter’s baseless remarks here

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For Agency & Public Review*

**EC-06 Comments By Wells, Posted 15 December 2004**

**SEE: C-10 Comments By Wells & Associates/Quality Hub, Inc. (W&A/QHI), Posted 7 December 2004**, because this posting seems to be a duplicate of that submission.

**EC-07 Comments By European Federation of Pharmaceutical Industries and Associations (EFPIA), Posted 15 December 2004**

**SEE: C-15 Comments By European Federation of Pharmaceutical Industries and Associations (EFPIA), Posted 15 December 2004**, because this posting seems to be a duplicate of that submission.

*Formal Review Of Comments Submitted To The FDA's Draft Guidance  
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**EC-08 Comments By American Association of Blood Banks (AABB),  
Posted 15 December 2004**

The AABB begins by stating:

"AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

AABB commends the Food and Drug Administration and especially the Quality System Guidance Development working group (QS working group) for putting this draft document together. AABB through its standards and accreditation processes emphasizes a quality systems approach to all aspects of blood banking and is pleased to note that FDA is also advocating a quality systems approach."

AABB's reviewed comments are as follows:

"It is AABB's understanding that, as a drug regulated under 21 CFR 211, blood and blood products are covered by the recommendations of this new draft guidance. Furthermore, it is our understanding that this document supplements the 1995 "Guideline for Quality Assurance in Blood Establishments" (11 July 1995) and does not supersede the earlier guideline.

This reviewer agrees with the commenter's understanding and notes that, *unless withdrawn and reissued as a "guidance,"* a true "guideline" takes precedence over any "guidance" because *true guidelines* are binding on both the Agency and the industry they guide — while guidance documents do not bind either – guidances only offer the Agency's current view of a way that a firm may approach the subject addressed in the guidance.

"AABB requests that clarification of the manner in which these two documents will be used together be emphasized in the final version of this guidance document. This is especially important should a conflict arise between the documents."

This reviewer defers to the Agency here since only the FDA can address "the manner in which these two documents will be used together."

*Formal Review Of Comments Submitted To The FDA's Draft Guidance  
For Agency & Public Review*

**C-16 Comments By Active Pharmaceutical Ingredients Committee (APIC),  
Posted 23 December 2004**

**SEE: EMC-06 Comments By Active Pharmaceutical Ingredients Committee  
(APIC), Posted 10 December 2004** because this posting seems to be a  
duplicate of that submission.

**END OF REVIEW OF COMMENTS POSTED  
UP TO 31 DECEMBER 2004  
TO DOCKET 2004D-0443**