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Comments On : " Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations"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On 15 November 2003, **FAME Systems** provided comments to this docket based on an in-depth reading of the FDA's "**Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations** [*G:\6452dft.doc 9/28/04*]."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current good manufacturing practice (CGMP), in general, and the drug CGMP and other regulations with which the Agency's draft guidance is required to be congruent.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 Saturday, 15 January 2005.
- Has prepared and electronically submitted **FAME Systems**' scientific and CGMP-conformance assessment of those formal comments.
- Has prepared and electronically submitted **FAME Systems**' revised draft of the published draft guidance that incorporates all of the constructive comments that were submitted: **a)** as an aid to the Agency in revising the originally published draft guidance **and b)** to shorten the review period for this guidance.
- Has prepared and is now electronically submitting the document that follows, entitled, "**Clarifying Notes For Revised Draft Guidance: Quality Systems Approach to Pharmaceutical CGMP Regulations**" that provides the reason for each change proposed in **FAME Systems**' prior revised guidance submission.

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, the changes are in a red Century font, and the original text is in a **Times New Roman** font.

Should anyone who reads this document find that its suggestions 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*, 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

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Clarifying Notes For Revised Draft Guidance:
Quality Systems Approach to Pharmaceutical CGMP Regulations

Line #	Clarification
5	Remove all instances of the word "draft" when used to modify this guidance because the guidance will be final when issued.
13	Removes the word "draft" and substitute "up-to-date" for "modern" because this term fits better than "modern."
14	Deletes the phrase, "and risk management," since the guidance clearly presents a "**Quality Systems Approach**."
15,19, 20	Capitalizes the initial letter in word "parts" in front of "210" (grammatical consistency).
19-20	Revises original sentence, "This guidance is not intended to place new expectations on manufacturers nor to replace the CGMP requirements," to improve grammar and readability and read, "This guidance is neither intended to place new expectations on manufacturers nor to replace the CGMP requirements."
20-21	Changes "Readers are advised to always refer to parts 210 and 211 to ensure full compliance with the regulations." to read "Readers are advised to always refer to Parts 210 and 211 to ensure full compliance with the regulations applicable to their situation" to appropriately limit the scope of the compliance required.
23	Removes the word "draft."
27-32	After "but not required," adds "The use of the words *can* or *may*, or derivatives thereof (i.e., *could* or *might*), in agency guidances means that alternatives are suggested or recommended, but not required. The use of the word *must* in agency guidances means that something is required by a specific statute or regulation (e.g., samples *must* be *representative* of the population [*lot* or *batch*] to satisfy 21 CFR Section [Sec. or §] 211.160(b))." to complete the explanation of the importance of the different regulation-related verbs used
35-36	Places titles in quotes.
38	Replaces "modern" with "state-of-the-practice" because the phrase is a better choice and implies proven technologies but not those that may not be fully proven ("state-of-the-art")
40	Removes the word "many" as it detracts from the statement being made.
42	Removes the word " modern" because it is superfluous and unneeded.
43	Replaces "CGMPs" with "CGMP regulations" because of the origin of the acronym, "CGMP," carries with it connotations that apply both the Federal Food, Drug, and Cosmetic Act (statute) and the regulations discussed one should refrain from pluralizing it as the plural of the phrase from which the acronym is derived, "current good manufacturing practice," is undefined.
48	Capitalizes the initial letter in the word "parts" when it appears before 210.
57	Removes the sentences, "For example, the CGMP regulations stress quality control. More recently developed quality systems stress quality management, quality assurance, and the use of risk management tools, in addition to quality control," because they are superfluous – they do not add value to the discussion – factually, the CGMP regulations stress CONTROL and not quality control, per se.
58	Removes the text "modern," because it does not add value and is superfluous.
61	Inserts "properly" between "if" and "implemented" to appropriately limit the statement being made.

Line #	Clarification
62	Changes "robust, modern" to "broad, robust" because the word "modern" is superfluous and the word "broad" is better suited for use here.
69-71	Changes "***Quality should be built into the product, and testing alone cannot be relied on to ensure product quality***." to "***Quality must be built into the product, the critical variable characteristics for all inputs must be adequately controlled, and, though clearly required by CGMP, representative-sample testing alone cannot be relied on to ensure product quality***" because it correctly states the realities about building quality into a finished pharmaceuticals (drug products) and corrects the obvious ambiguities in the original statement.
79	Replaces "CGMPs" with "CGMP regulations" because of the origin of the acronym, "CGMP," carries with it connotations that apply both the Federal Food, Drug, and Cosmetic Act (statute) and the regulations discussed one should refrain from pluralizing it as the plural of the phrase from which the acronym is derived, "current good manufacturing practice," is undefined.
80-81	Changes "including ISO 9000" to "including those addressed in the 'ISO 9000' set of standards" to reflect the fact that the ISO quality system is addressed in a set of standards and not in "ISO 9000" *per se*.
85-86	Adds the restrictive phrase "provided the applicable CGMP minimums are met" to the end of the sentence ending, "…is very desirable," to appropriately limit the statement to CGMP-compliant quality systems.
87	Replaces the word "modern" with "today's" because it is more appropriate here
94	Inserts the word "comprehensive" between "A" and "quality" to qualify the type of quality system here.
97	Replaces the word "A" with the phrase "The particular" for more clarity here.
101	Replaces the word "manufacturers" with the phrase "those engaged in any facet of the manufacture" because the change better describes the scope of the guidance
104	Inserts the word "the" between the words "of" and "products" to improve the reading of the sentence.
106-108	Revises the 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" to read "This document is **neither** meant to create new expectations for pharmaceutical manufacturing that go beyond the requirements laid out in the current regulations **nor** intended to be a guide for the conduct of FDA inspections" both to improve its readability and to remove unnecessarily duplicative wording.
109	Capitalizes the initial letter in word "parts" in front of "210" (grammar).
112	Replaces the wording "…CGMP regulations, and FDA's inspection program …" with the wording " … CGMP regulations. Thus, the FDA's inspection program …" because the connective ", and" is not appropriate grammar here.
114	Replaces the phrase "this draft" with "This" to remove the inappropriate word "draft" which should only be used in the introductory titles and not in the text when referring to "this guidance."
117	Replaces the cryptic, "Major sections of the model include the following:," with the improved more readable and clearer, "Therefore, the major sections of the model used in this guidance are:"

Line #	Clarification
122	Replaces the sentence, "Under each of these sections the key elements found in modern quality systems are discussed," with the sentence, "Within each of these sections, the key elements found in today's quality systems are discussed" to improve the sentences flow and replace the word "modern" with a more appropriate modifier, "today's."
127-128	Replaces the sentence, "A glossary is included at the end of the document," with the sentence, "A glossary is included at the end of the document for those not familiar with the CGMP, process, quality, and statistical terms defined therein," to provide the reason for including a glossary and describe the kind of terms defined therein.
129	Changes the section's header to "**CGMP AND THE CONCEPTS OF TODAY'S QUALITY SYSTEMS**" to improve and broaden the acronym's reach and to replace the word "**MODERN**" with the more appropriate "**TODAY'S**"
130-134	Adds the paragraph, "CGMP is the acronym for "**current good manufacturing practice**," as that phrase is used in 21 U.S.C. Section 351(a)(2)(B), the statutory foundation underlying the CGMP regulations for drugs and finished pharmaceuticals that: **a)** establish the requirement *minimums* for the manufacture, processing, packing or holding of drug products and **b)** are the focus of the quality systems approach used in this guidance." to include some appropriate discussion of term "**CGMP**" and its statutory origins in the text.
135	Modifies the sentence, "Several key concepts are critical for any discussion of modern quality systems," to read, "Similarly, several key concepts are critical for any discussion of today's quality systems," so that it flows from the inserted text and, with the replacement of "modern" with "today's," to improve the text's currency.
135-137	Revises the sentence, "The following concepts are used throughout this guidance as they relate to the manufacture of pharmaceutical products," to read, "The following concepts, as they relate to the manufacture of pharmaceutical products, are the important basis ideas used in this guidance," to improve the sentence's readability and better align the statement made with the guidance provided.
140-143	Revises the sentence, "For the purposes of this draft guidance document, the phrase *achieving quality* means achieving these characteristics for the product," to read, "For the purposes of this guidance document, the phrase *achieving quality* means achieving these characteristics for all the product units from the time these units are released until after the units have passed their expiration date," to remove the word "draft," and improve the definition to remind the reader that the goals are for all of the units from release until they pass their expiration date.
146-147	Revises the phrase, "… to consistently ensure a predefined quality at the end of the manufacturing process," to read, "… to consistently ensure each unit produced meets all of its predefined quality criteria at the end of the manufacturing process," so that what CGMP truly expects here is clearly stated.
151-152	Puts title of document in quotes.
154-155	Revises the sentence, "Risk assessment is also used in determining the need for discrepancy investigations and corrective action," to read, "When risk assessment is used more formally by manufacturers, it should be implemented within a quality system framework," to improve what is being stated within the context of the discussion in this paragraph.

Line #	Clarification
155-161	Adds a paragraph, "It should be noted that the CGMP regulations for finished pharmaceuticals (21 CFR Part 211) establish risked-based minimums for components, processes, in-process materials, and drug-product quality assessments 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 quality that is well below today's recognized 'de facto' accepted performance standard for quality excellence ('Six Sigma')," to: **a)** make it clear that the CGMP regulations are themselves risk-based, **b)** state the 1978 minimum standard for quality **and c)** state today's "current" minimum standard for "good" quality in a CGMP environment.
162-177 & 185-219	Adds a new Section "**D,**" titled "**Systems Controls**" that references a figure (Lines 185-219), titled "**OVERVIEW OF THE *CONTROLS* STRUCTURE IN 21 CFR PART 211**," to address a major omission in the original draft.
178	Changes the existing Section "**D**" to "**E**" and the title from "**CAPA (Corrective and Preventive Action)**" to "**CAPA (Corrective Action and Preventive Action)**" so that the text matches the acronym "**CAPA**."
180	Changes the phrase, "prevent recurrence," to "prevent their recurrence," so that it is clear what recurrence is intended to be prevented.
181	Replaces the word "as" with the phrase, "in terms of," to improve the clarity of the sentence with respect to how CAPA is addressed in quality systems.
181	Inserts the sentence, "Those three concepts are:," to connect the paragraph to the list of terms.
221	Changes Section "**E**" to "**F**" to reflect the prior insertion of an additional section
223-226	Insert the sentence, "Ideally, change control should be incorporated into an ongoing journey-based approach to generating and maintaining a process that continually operates in its validated ("proven valid") state," so that the proper placement of Change Control within the context of ongoing production is addressed
226-227	Changes the sentence, "The major implementation of change control in the CGMP regulations is through the assigned responsibilities of the quality control unit," to read, "The major implementation of change control in the CGMP regulations is expressed in the responsibilities assigned to the quality control unit," to better express what the applicable CGMP regulations actually state – responsibilities assigned.
227-229	Changes the sentence, "Certain manufacturing changes (e.g., changes that alter specifications, a critical product attribute or bioavailability) require regulatory filings and prior regulatory approval (601.12 and 314.70)," to read, "In addition, certain manufacturing changes (e.g., changes that alter specifications or critical product characteristics, including bioavailability) require regulatory filings and prior regulatory approval (see §§ 601.12 and 314.70)" to improve paragraph flow, sentence readability, and citation accuracy and consistency.
231-234	Changes the sentence, "In this guidance, *change* is discussed in terms of creating a regulatory environment that encourages change towards continuous improvement," to read, "In this guidance, *change* is discussed in terms of creating a regulatory environment that encourages change and continual improvement in the process, without adversely affecting in-process integrity, or the quality of the product," to reflect the reality that change is, by nature, discontinuous, and to express the process and product limitations on change in a CGMP environment.

Line #	Clarification
234-238	Changes the sentence, "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," to read, "This means a manufacturer is empowered to make predetermined changes in response to the permissible variability of materials used in manufacturing and otherwise optimize the process 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," so that it is clear that: **a)** these empowered "material variability" changes should be limited to those that have been predetermined to produce acceptable product within the permissible range for the variability is said materials and **b)** those that otherwise "optimize the process" should be based on the appropriate use of suitable statistical control techniques.
239	Changes Section "**F**" to "**G**" to reflect the prior insertion of an additional section.
240	Changes the word "modern" to "current" because this is a better word choice given the context of this sentence.
243-244	Changes the phrase to read, "… among the quality control (QC), quality assurance (QA) and regulatory affairs (RA) functions," to reflect the reality that, in many organizations, the quality control unit's responsibilities and authorities are split among three functional groups, QC, QA, and RA.
245-249	Changes this bullet, "QC usually consists of testing of selected in-process materials and finished products to evaluate the performance of the manufacturing process, and to ensure adherence to proper specifications and limits," to read, "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, and to determine the acceptability of each lot or batch for release," so that the text better matches typical QC responsibility assignments.
250-253	Changes this bullet, "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," to read, "QA primarily includes the review and approval of all procedures related to production, maintenance, and review of associated records, and auditing, and overseeing trend analysis evaluations. In some firms, QA also determines the acceptability of each batch or lot for release," so that the text better matches typical QA responsibility assignments
254-255	Adds this bullet, "RA typically acts as the quality function's bi-directional interface between the other quality functions and the FDA," so that the text reflects typical RA responsibility assignments
256-257	Changes the sentence, "This guidance uses the term *quality unit* [4] (QU) to reflect modern practice while remaining consistent with the CGMP definition in 21 CFR 210.3(b)(15)," to read, "This guidance uses the term *quality unit* [4] (QU) to reflect current practice while remaining consistent with the CGMP definition in 21 CFR Sec. 210.3(b)(15)," to: **a)** substitute the more appropriate word, "current," for the word, "modern," and **b)** correct the cited section of the regulations to include a Section abbreviation (Sec.).

Line #	Clarification
257-260	Changes the sentence, "The concept *quality unit* is also consistent with modern quality systems in ensuring that the various operations associated with all systems are appropriately conducted, approved, and monitored," to read, "The concept *quality unit* is also consistent with current quality systems in ensuring that the various operations associated with all systems are scientifically sound, appropriate, and appropriately approved, implemented, conducted, modified, and monitored," to: **a)** substitute the more appropriate word, "current," for the word, "modern," **b)** include the need for all to be first, *scientifically sound* and second, *appropriate*, critical realities in a CGMP-compliant quality system, and **c)** include the added terms.
260-263	Changes the sentence, "The CGMP regulations specifically assign the quality unit the authority to create, monitor, and implement the quality system," to "The CGMP regulations specifically assign the quality unit the authority to review and approve the quality system and any change thereto," to accurately reflect the specific authorities that are actually assigned in the CGMP regulations.
265-267	Changes the text to read, "Under a robust quality system, the product and process development units, manufacturing units, and the quality unit can remain independent, but are all still included in the total concept of producing quality products," so that the product and process development units are explicitly mentioned and the verb in the conjunctive phrase is changed from the indefinite "be" to the appropriate present tense active verb, "are."
267-272	Inserts the following text, "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," because, *in the context of this discussion*, this is where this text fits.
273-274	Changes the text to read, "Other CGMP assigned responsibilities of the quality unit are consistent with current quality system approaches (see § 211.22) and include:" to: **a)** replace the word "modern" with the more appropriate word "current" and **b)** add the "and include:" to connect the sentence to the list that follows it.
275-277	Inserts, as the first 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," so that the these critical controls areas are appropriately included in the list because these are areas that, as the original draft's omission indicates, often get overlooked.
282	Inserts the phrase, "incoming and," between the words "rejecting" and "in-process" and adding a comma "," after the word "materials" to: **a)** include incoming materials and **b)**, by inserting the comma, address the difference between materials and drug products.
285	Inserts the phrase, "overseeing the investigation of," between the words "and" and "any" to reflect the reality that their function is one of oversight (review and approve) not necessarily doing the requisite investigations.
287	Adds the bullet, "Ensuring a CGMP-compliant quality review process is in place," because including it is clearly needed
288	Changes Section "**G**" to "**H**" to reflect the prior insertion of an additional section.
289-300	Replaces the word "manufacturing" preceding the word "systems" to the word "operational" each time it occurs in this paragraph because this change appropriately broadens the reach of the systems to include, as it should, those organizations that only process and/or pack drug products.

Line #	Clarification
294	Replaces the phrase, "… that are linked and function within it," with the phrase, "… that are linked to, and function within, it," to improve the grammar while minimizing the wordiness from "… linked to it and function within it."
300	Replaces the awkward (in verb tense and wording) phrase, "… will also serve to help …," with the guidance-appropriate and clearer phrase, "… should also help …,"
301	Changes "**Fig. 1**" to "**Fig. 2**" to reflect the prior insertion of a figure here.
323	Changes the verb "will" to "may" because that is the verb that should be used here because the magnitude of requirements indicated is not absolutely certain.
324	Changes the verb "will" to "should" because the outcome suggested cannot be guaranteed.
326	Inserts the word "properly" between the words "if" and "implemented" because the outcome suggested is contingent upon a proper implementation.
327	Inserts the phrase, "more than," between the words "of" and "acceptable" because that level of consistent quality is the minimum that should ensure that, under worst-case conditions, the product should have a high probability of meeting its acceptance criteria.
341	Deletes the unnecessary and inappropriate word "modern" in front of the phrase "quality systems"
345	Replaces the word "Modern" with "Today's" at the start of this sentence because it is a more appropriate word choice.
348	Changes the phrase, "Management has ultimate …," to read, "Management also has the ultimate …," to improve text flow and sentence readability.
353	Deletes the unnecessary and inappropriate word "modern" in front of the phrase, "quality system."
356-357	Changes the original sentence to read, "Senior managers set implementation priorities and oversee the development of action plans," because senior managers oversee, but may not necessarily actually develop, such plans.
357-358	Changes the original sentence to read, "These managers can also provide support to the quality system by:," because the revisions material improve the flow, grammar, and message in this sentence and, as it should, connect it to the previous sentence and its subject.
364	Replaces the unnecessarily wordy and less-than-clear phrasing, "... the quality system and ensure its global implementation throughout the organization (e.g., across multiple sites)," with the concise and clear text, "their firm's global quality system. Managers should have an understanding of all applicable regulations (US, other country and international) and apply that insight to ensure the appropriate global implementation of their firm's quality system throughout the organization (e.g., across multiple sites)," that clearly puts the proverbial "ear on the pot" where it belongs in an FDA guidance by placing the US regulations at the head of the list.
376-378	Changes the text, "Senior managers have the responsibility to ensure that the organization's structure is documented," to read, "Management has the responsibility to ensure that the organization's structure is appropriately documented. In this regard, all responsibilities and authorities should be documented (e.g., job descriptions and organization charts)," to: **a)** broaden the responsibility to all levels of management, and **b)** explicitly add the expectation that all responsibilities and authorities should be documented.

Line #	Clarification
381-383	Augments the original text by adding, "Managers are also responsible for ensuring that the documented procedures match actual practice and that all who report to them are properly trained and follow all applicable procedures," because these are also responsibilities that managers have.
390-392	Revises the phrase, "…quality system addresses the minimum requirements of CGMP regulations as well as the needs of the manufacturer," to read, "…quality system meets or exceeds the requirement minimums of the applicable CGMP regulations as well as meets the other needs of the organization," because the revisions clearly improve realities of a quality-oriented quality system, appropriately broaden its reach, and, by including the word "other," clearly states that meeting or exceeding the requirement minimums of the applicable CGMP regulations is a need for all FDA-regulated drug-product organizations.
393-395	Replaces the phrase, "… quality system they design and implement provides clear organizational guidance and facilitates systematic evaluation of issues," with the phrase, "… quality system that is designed, approved and implemented provides clear organizational guidance and facilitates systematic evaluation of issues," to address the reality that the quality system is not solely designed, approved and implemented by senior managers.
399	Replaces the phrase, "…policies to …," with the phrase, … directives that …," to reflect the reality that some firms use more than policies in their implementations of their quality system.
401	Inserts the phrase, "and other documents" between the words "procedures" and "needed" because other documents, like work instructions, reference texts, textbooks, and recognized standards (ANSI, AOAC International, ASQ, ASTM, ISO, and USP), are also used here.
403-404	Adds a bullet that states, "The proofs that establish that the quality system meets the requirement minimums of the applicable CGMP regulations," because the CGMP regulations use of the verb "establish" or the phrase "establishment of" generate the requirement that a CGMP-compliant firm is required to have ***proofs*** that their controls at least meet the applicable CGMP minimums
405-408	Changes the sentence, "It is recommended under a modern quality systems approach that a formal process be established to submit change requests to directives," to read, "It is recommended, under a quality systems approach, that a formal process be established to address requests for changes to all directives (e.g., mission, vision and values statements, policies, plans, specifications, standard operating procedures, and work instructions) covered by the firm's quality system," because: **a)** the revised text broadens the coverage to beyond the mere submission of change requests and **b)** lists the types directives that should be covered by the quality system.
409	Removes the word "record" from the phrase, "… document record control …" because the word in question is out of place here.

Line #	Clarification
411-418	Changes the sentence, "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))," to read, "This approach is consistent with the CGMP regulations, which require manufacturers to establish scientifically sound and appropriate written controls for specifications, plans, and procedures (21 CFR Sec. 211.160) that direct operational and quality system operations, and to ensure that these directives are accurate, appropriately reviewed and approved, available for use, and followed (see the CGMP regulations at §§ 211.22 (c) and (d), 211.80(a), 211.100 (b), 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), (b), and (c))," to: **a)** include the explicit need to establish scientifically sound and appropriate written controls, **b)** include the appropriate CGMP cites for all of the "activities" addressed in the text in question, **c)** replace the word "activities" with the word "operations," and **d)** add the clear requirement that written directives must be followed.
420	Deletes the unnecessary and inappropriate word "modern" in front of "quality system."
437	Inserts the phrase, "the organization's," between the words "with" and "strategic" to improve the statements clarity.
441-443	Changes the text, "Such a review typically includes both an assessment of the product …," to read, "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 …," to: **a)** expand the review's coverage to include, as it should, incoming and in-process materials, the finished products and the process used for each drug product or product family, and **b)** make it clear that such reviews should assess each such factor..
451-452	Changes the phrase, "…or a recurrence," to read, "…or the recurrence of previous problems," to improve the clarity of the message intended to be conveyed here.
453	Replaces the word "Any" with the phrase, "The status of any" to widen what should be reviewed and better reflect what is generally reviewed.
456-457	Changes the bullet, "Product characteristics meet the customer's needs," to read, "Product characteristics meet both the applicable CGMP minimums and the other customers' needs," to reflect the CGMP-compliance reality and reflect that, besides the FDA's CGMP-compliance requirements, the customers, including the FDA, have other needs.
458	Inserts the phrase, ", in general, ," between the words "should" and "take" to appropriately generalize the statement.
468-481	Adds a Subsection "6," titled, "*Audit Operations to Ensure Compliance*," to address the need for audits.
483-485	Changes the sentence, "Manufacturers should always refer to the specific regulations to ensure that they are complying with all regulations," to read, "Manufacturers, processors, and packers should always refer to the specific regulations to ensure that they are complying with all regulations that apply to their firm," to: **a)** broaden the scope of the firms covered, and **b)** to limit the regulations scope to those that are applicable to a given firm.
485-486	Corrects minor list errors in the table that follows Line 486 and adds a row for "System Audit" and its CGMP references information.
489-490	Inserts the word "applicable" between the words "the" and "CGMP" to limit the scope of the regulations that a firm's quality system must address.
496-497	Changes the text, "… a quality product," to read, "… a quality product in compliance with the applicable CGMP (see §§ 211 Subparts C & D)," so that the applicable CGMP is referenced.

Line #	Clarification
498-500	Changes bullet to read, "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 & 211.122)," to improve the accuracy of the text and include the specific supporting CGMP regulation references for this bullet.
501-502	Changes bullet to read, "For processing the materials in a CGMP-compliant manner to produce the finished drug product (see §§ 211 Subpart F)," to improve the accuracy of the text and include the specific supporting CGMP regulation references for this bullet.
503-504	Adds a bullet that states, "For packaging and labeling the finished drug product into finished packaged drug product (see §§ 211.125, 130, 132, 134, 137 and 160(b)(1))," to directly address packaging and labeling
505-513	Changes bullet to read, "For the CGMP-compliant evaluation of an appropriate number representative samples of incoming (see §§ 211.84(d), 211.87, 211.94(d), 211.122(a) and 211.160(b)(1) and in-process materials (see §§ 211.110 and 211.160(b)(2)) and the finished drug product (see §§ 211.160(b)(3), 211.165, 211.166 and 211.167), including the collection, storage, and examination of representative samples of incoming materials (see §§ 211.160(b)(1)), in-process materials (see §§ 211.160(b)(2)), stability samples (see §§ 211.160(b)(3) and 211.166), reserve samples (see § 211.170) and, where required to meet the requirements in 21 CFR Sec. 211.198, complaint samples," to: **a)** improve the accuracy of the text, **b)** include complaint sample examinations, and **c)** include the specific supporting CGMP regulation references for this bullet.
514-516	Adds a bullet that states, "For the CGMP-compliant acceptance or rejection for release of each batch or lot of drug product (see § 211.165) using representative sample evaluations (see § 211.160(b)(3)) and statistical quality control (see § 211.165(d))," to address CGMP-compliant drug-product release evaluation resources that include the requirements for representative sample evaluations and statistical quality control.
521	Changes the compound word "cross-cutting" to "cross-functional" because it is better choice in the context of a unified approach.
531	Changes the word "continued" to "continuing" to improve the congruence of the text with the wording of the CGMP requirement that also applies.
532-533	Adds the text "(see § 211.25(a))" at the end of the sentence to include the appropriate reference to the applicable CGMP regulation.
544	Changes the word "supervisory" to "operations" because it is a broader term that includes managers that do not supervise a defined group of direct reports.
549	Inserts the word "defining" between the words "for" and "specific" to specify the responsibility (defining) of the technical experts vis-à-vis specific requirements.
554-557	Changes the text to read, "According to the CGMP regulations, equipment must be appropriately located, qualified, calibrated, cleaned, maintained and operated in a state of control to prevent contamination and mix-ups (see §§ 211.63, 211.67 and 211.68). [**Note:** The CGMP regulations require a higher standard for calibration and maintenance than most generic quality system models.]," to: **a)** include installation (located) and operated in control, **b)** correct the CGMP regulation citation to the standard format used previously, and **c)** convert the second sentence into a note.
558-559	Changes the citation from "§§ 211.63, 211.67, 211.68" to "see 21 CFR 211 Subpart D—Equipment" to: **a)** simplify and broaden the citation and **b)** align it with like citations
559	Changes the phrase "while most quality systems focus only on testing equipment" to the phrase to "while the majority of quality systems focus more on testing equipment" so that the text is a better match to reality.

Line #	Clarification
560-568	Lines added to address the suitability of ISO 17025 as a basis for a comprehensive quality system suited for pharmaceutical operations.
569	Changes the Subsection "*4*" title to "*4. Control of Outsourced Operations and Suppliers of Materials*" to improve its agreement with the subject matter discussed.
574-577	Lines added to address QCU control of contractors.
578-584	Changes the text, "Under a quality system, the manufacturer ensures that the contract firm is qualified. 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 standards should not conflict. It is critical in a quality system to ensure that the contracting manufacturer's officers are familiar with the specifics requirements of the contract," to read, "Under a quality system, the product manufacturer ensures that the contracted firm is qualified through an on-site audit and other means, as appropriate. 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. 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," to: **a)** improve the narrative, **b)** specify how qualification is to be accomplished, **c)** introduce the use of the term, "contracted" as a modifier to the word "firm," **d)** use the wording "responsible senior managers (or officers) for the …" in place of the draft's "officers …," and **e)** the use of the word "understand" in place of the draft's convoluted phrase, "are familiar with."
586-590	Changes the paragraph, "As the following table illustrates, the CGMP regulations are consistent with the elements of a quality system in many areas in this section. However, manufacturers should always refer to the specific regulations to ensure that they are complying with all regulations," to read: "As the table on the following page illustrates, the CGMP regulations are consistent with the elements of a quality system in many of the areas discussed in this section. However, manufacturers, processors, and packers should always refer to the specific regulations to ensure that they are complying with all regulations that apply to their organization," to: **a)** change the text to reflect the table's being on the next page, **b)** improve the construction of the text, **c)** widen the scope to cover those who engage in any facet of the pharmaceutical industry that is regulated by the FDA, and **d)** limit the scope of the quality system to those that apply to the covered activities in which they are engaged.
597-598	Corrects the minor grammatical listing errors and the title of Subsection "4" to parallel the title in the text.
600	Deletes the unnecessary and inappropriate word "modern" in front of "quality system."
603-611	Changes the text, "It is important to establish responsibility for designing or changing products. Documenting associated processes will ensure that critical variables are identified. This documentation includes:," to read, "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 be difficult to accomplish. Documenting associated processes should ensure that all critical variables are identified and, to the extent required, properly controlled. This documentation should include:," to: **a)** clarify the responsibility placement for designing and changing products, **b)** add verbiage to address where to begin the "building in" of quality and the justification appertaining thereto, **c)** improve the sentence addressing documenting, and **d)** appropriately change the verb tense in the last sentence.

Line #	Clarification
620	Replaces the word "process" with its plural "processes" to make it grammatically agree in number with the other items in mentioned in this bullet
621	Corrects grammar by placing "IV.A. Management," in quotations as follows: "IV.A. Management,".
622-623	Moves the verb, "are" to after the parenthetical phrase ending "… scientists)" and adding the phrase, "scientifically sound and appropriate," because this is the critical job (responsibility) that the managers of "technical experts" have.
624-627	Changes the text, "In the pharmaceutical environment, experts would have an understanding of pharmaceutical science, risk factors, and manufacturing processes as well as how variations in materials and processes can ultimately affect the finished product," to read, "In the pharmaceutical environment, experts should have an understanding of the applicable CGMP minimums, pharmaceutical science, risk factors, and manufacturing processes as well as how variations in materials and processes can ultimately affect the finished product and/or the attainment of the CGMP minimums," to: **a)** correct the first sentence's verb from "could" to "should" as guidance should do, **b)** include the critical requirement (the applicable CGMP minimums), and **c)** address the key issue of attainment of the CGMP minimums.
627-630	Inserts the sentence, "One key CGMP minimum that must be appropriately addressed in development is the requirement that each batch must be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient (see § 211.101(a))," because this is a key CGMP requirement that seems to be ignored.
631	Changes the title of the Subsection "2" from "*Monitor Packaging and Labeling Processes*" to "*Define and Control Inputs*" (from the less accurate title "*Examine Inputs*" in the original draft), and move the associated text from its relative location in the draft to after this title.
632-639	Changes the first paragraph in the moved text to read, "In current quality systems models, the term *input* 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. *Materials* 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," because: **a)** these changes improve the readability of the text, **b)** broaden the definition of input to match the scope of the CGMP regulations for drug products, and **c)** make the parenthetical list of examples more inclusive.
643-648	Changes the draft's text, "The CGMP regulations require either testing or use of a certificate of analysis (COA) plus an identity analysis (see §§ 211.22 and 211.84)," to read, "The CGMP regulations require either: **a)** full testing, or **b)** use of a report of analysis (ROA), commonly called a certificate of analysis (COA) by the industry, provided that at least one specific identity test is conducted on representative samples of the 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)," to correct the misstatements in the original draft's text
651	Changes the acronym used from "COA" to the CGMP-related acronym, "ROA" because that terminology better matches the language in the applicable CGMP regulations.

Line #	Clarification
653-663	Adds text to clearly spell out the factual expectations of the applicable CGMP regulations in some detail because the draft and the industry continually get the requirement minimums for components wrong.
665-667	Adds text, "In addition, the manufacturer's quality control unit is responsible for approving the tests and specifications for all materials (see § 211.22(a))," to reinforce the "inputs" role of the quality unit here.
669	Inserts the phrase, ", or its contracted qualified agent, ," between the words "manufacturer" and "can" to indicate the permissible use of a qualified third-party auditor.
674-677	Changes the parenthetical sentence, "(A specific identity test is still required in § 211.84(d)(1).)," to a bracketed note, "[**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 are still required (see § 211.84(b) and § 211.84(d)(2)).]," to: **a)** remind the reader that of the sampling and identity testing requirements are predicated upon having taken representative samples, and **b)** correct the regulation citation appropriately.
685	Delete the word "certain" before the word "changes" because the QCU is responsible for reviewing and approving all changes.
686	Changes an open parenthesis, "(," before "see" to an open bracket, "[," and inserts a close bracket, "]," between the two ending close parenthesis, "))," to correct punctuation.
689	Change the title of Subsection "3" from "*Examine Inputs*" in the original draft to "Perform, Monitor and Validate Operations," include "validate" language in the title and the associated text, and relocate the text after the title because this is where this material fits better.
690-692	Change the sentence to read, "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 (see § 211.110(a))," to: **a)** remind the reader that the quality system implemented should be CGMP-compliant, **b)** explicitly include the "validate" text" and **c)** incorporate the parenthetical citation of the applicable CGMP regulation.
695	Insert the word "untested" between the words "the" and "finished" to make it clear that the purpose of the evaluations performed is to ensure that the untested portion of the batch meets its acceptance criteria based on the statistical inference prediction derived from the appropriate statistical evaluation of the results obtained from testing an appropriately representative number of drug product units.
698	Delete the unnecessary and inappropriate word "modern" in front of "quality system."
704-709	Change the text 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 [14] 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 consistently meeting its established specification targets," to: **a)** place the referenced section identifier in quotes, **b)** change the text to indicate an initial validation of the process, and **c)** offer alternative approaches to establishing that the process remains in its "is valid" state and the product produced consistently meets or exceeds all of its acceptance criteria.
710	Change the initial part of the text to read, "In a quality system, the initial phases of process validation provide preliminary proof, …," to align what is being stated with the factual reality the initial phases of validation only provide preliminary evidence about the soundness of the process and the consistency of the product produced by that process when it is operating in control.

Line #	Clarification
713	Deletes the word "modern" before "equipment" because the text applies to all equipment.
716	Replaces the phrase, "*ongoing production*," with the phrase, "the *entire life-cycle*," to address what a firm can actual deal with.
718-719	Appends the phrase, "for as long as that process is used," to define the continuation period.
738	Inserts the word "homogeneously" between the words, "until" and "mixed."
744-759	Adds to paragraph to address "batch acceptance for release for distribution" and "*batch-representative statistical quality control,*" respectively
761	Inserts the word "critical" between the words "their" and "parameters" to limit the scope for the parameters that must be assessed.
769-770	Changes the text to read, "Process understanding increases with experience and helps identify the need for changes that can improve the process or the quality of the drug product," to convey the factual limitations on changes that should be pursued under a CGMP-compliant quality system.
772-773	Changes the bullet to read, "Are the methods for the evaluation of representative samples and data collection properly documented?," to again emphasize the need for representative samples and detailed methods.
774	Changes the bullet to read, "When in the product's production cycle will the data be collected?," to the practical reality that data is acquired in conjunction with product production from predetermined locations during the operation of various stages of each FDA-regulated process.
776-777	Changes the bullet to read, "When should analysis and evaluation (e.g. trending) of the data collected be performed (see section "V.E.1.")?," to: **a)** omit the restriction to laboratory data, **b)** limit the requisite studies to the data collected, and **c)** correct the grammar used in the parenthetical citation to match that of the previous citations and section references.
779	Changes the beginning of the sentence to read, "Current quality system approaches indicate that …, to: **a)** remove the word "modern" because it does not belong here, and **b)** change the subject and verb in the sentence from the singular to the plural.
783-784	Replaces the improper acronym "CGMPs" to the proper form "CGMP regulations" for the reasons given in the beginning of these notes
787-789	Insert the word "see" before the "§" in each parenthetical CGMP citation to bring then up to the documentation standard used previously.
788	Revises the phrase, "laboratory controls," to state, "the controls themselves," to recognize that the controls in question extend beyond the laboratory.
790-791	Changes the phrase, "that may be affected based on understanding of the process," to read, "that, based on the firm's understanding of the process, may be affected," to improve the sentence's readability.
799-805	Changes the text, "Invalidation of test results should be scientifically and statistically sound and justified," to "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. [**Note:** To facilitate the critical evaluation of data, the manufacturer's laboratory and other evaluation operations (in-house and contract) should adopt systems that identifiably link the specific equipment, materials, personnel, method execution steps, and other factors that may affect outcomes to each result value generated to the result values found.]," to: **a)** correct the illogical "scientifically and statistically sound," **b)** clearly state that an actual cause should be identified, and **c)** add a note suggesting that identifiably liking all items used to generate a result should be traceably linked to that data.

Line #	Clarification
807	Inserts the phrase, "and storage," between the words "shipment" and "requirements" to address special conditions that are sometimes required for both aspects of the handling of the drug products.
813-814	Changes the beginning of the sentence, "Process capability assessment can serve as a basis for," to read, "Ongoing *minimum process capability* assessment can serve as a basis for establishing that the process is still in a validated state as well as for," to: a) indicate that this activity must be ongoing, b) recognize that ONLY the uncertainty corrected process capability values (expressed in terms of the *minimum process capability*) should be used to make such assessments, and c) recognize minimum process capability values may be used to support the ongoing validity of the firm's production processes.
817	Changes the Subsection number from "*2*" to "*4*" and relocate the draft's text appropriately.
819	Insert the word "most" between the words "in" and "quality" to allow for the reality that some quality systems that address some aspects of packaging and labeling.
820	Inserts the text, ", processors and packers," between the words "manufacturers" and "always" to allow for the fact that the CGMP regulations also cover processors and packers of drug products.
821	Changes the phrase, "…regulations at 21 CFR 211 Subpart G," to read, "… regulations in 21 CFR 211 Subpart G for their quality systems guidance in these areas," to: a) recognize the reality that the regulations in question are in 21 CFR Subpart G and b) state the reason for the reference.
822	Replaces the word "modern" with the word "current."
830-838	Adds a Subsection "*5*" to address the assessment of drug product stability and expiration dating.
839	Changes Subsection number from "*5*" to "*6*" and relocates text to fit revised structure of this Section.
842-847	Changes the text, "CFR 211.192). To ensure that a product conforms to requirements and expectations, it is important to measure process and the product attributes (e.g., specified control parameters strength) as planned," to read, "CFR § 211.192). To ensure that a product conforms to requirements and expectations, it is important to assess 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," to: a) correct the CFR citation, b) address the reality that assessment of the uniformity of the process and the product is the key activity and not measurement per se, c) note that one evaluates critical process parameters and product characteristics, and d) provide appropriate examples.
847-848	Changes the text to state, "Discrepancies may be detected during any stage of the process by an employee or a validated computerized system designed to detect discrepancies," to include the possibility for a suitable validated computer to be used in lieu of a person.
857-860	Changes the sentence to read, "If the nonconformity is significant, based on consequences to process control (in terms of conformance to parameter set points, safety, efficiency, and yield), and product acceptability (in terms of conformance to specifications, safety and efficacy), it is important to evaluate how to prevent its recurrence," to: a) properly address process control and product acceptability.
863-865	Changes the sentence to read, "Remedial action may include correcting the nonconformity; or, with proper authorization and documentation, allowing the product to proceed, or, if allowable, using the product for another application; or rejecting the product," to: a) to include the need for documentation, and b) making it clear that using the product for another application may not be allowed.

Line #	Clarification
865-867	Changes the sentence to read, "If an individual product that does not meet requirements has been released, the Agency must be notified "immediately" [19] and the product should be recalled," to make it clear that notification is required (generally within 3 working days of the finding of a **possible** problem), but recall is a voluntary action that should be undertaken.
869	Inserts the heading, "*7. Improve Processes*" and uses the text which follows that heading to address the subject stated in the heading
870	Deletes the superfluous word "modern" and changes the word "processes" to the phrase, "process steps," to: a) improve the sentence's wording and b) reduce the granularity from the level of the discussion from the "whole process level" to the "process-step level."
878-879	Inserts the word "ongoing" before the word "design"; inserts the phrase, "and design implementation," after the word "design"; and changes the word "process" to "processes" to: **a)** ensure that these are treated as ongoing activities and **b)** make it clear that the firm's controls should be maintained throughout the continuing implementation phase.
880-885	Inserts introductory text for the table that addresses "Manufacturing Operations."
886-887	Modifies text in the table to correct minor citation issues and adds the rows for the three (3) Subsections added in the text.
897	Replace the phrase, "…of the state of control of a process," with the phrase, … that controls are losing effectiveness," to generalize what the analysis of data can do with respect to process control.
897	Changes the verb from "will" to "may" because the true value of the information cannot be predicted.
899-904	Changes the sentence, "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," to read, "Although the minimum periodic review required in the CGMP regulations (see § 211.180(e)) calls for review of a representative number of initiated batches, released or not, of each product along with a review of complaints, recalls, returned or salvaged drug products, and investigations conducted under § 211.192 for each drug product on an annual basis; quality systems calls for trending on a regular basis," to: **a)** point out that "annual review" is the least frequent permissible period, **b)** correct the citation's format to match the others in this guidance, and **c)** correct the language to present all that the CGMP regulations require to be evaluated.
905	Replaces the word "modern" with the word "current" because it is a better choice here.
906	Changes the text, "whole; this is consistent," to read, "whole. This concept is consistent," to: separate the two parts of the original and improve the readability of the text here.
907	Insert the phrase, "the organization's," between the words "focus" and "internal" to state whose internal audits the guidance is talking about.
908	Replaces the word "*Audit*" with "*Audits*" to improve the agreement between the title's language and the text's subject matter.
935	Replaces the phrase, "a reiterative," with the phrase, "an iterative," to correct the wording to reflect the reality.
936	Changes the word "management" to "assessment," the topic being discussed.
966-967	Changes the sentence, "The effectiveness and efficiency of the quality system can be improved through the quality activities described in this guidance," to read, "Management should improve the effectiveness and efficiency of the quality system itself by appropriately adopting the applicable quality activities described in this guidance," to: **a)** improve the guidance's sentence structure, and **b)** state who can improve, and how to improve, the effectiveness and efficiency of the quality system adopted.

Line #	Clarification
968-970	Changes the sentence, "It is critical that senior management be involved in the evaluation of this improvement process (section IV.D.3.)," to read, "However, it is critical that senior management be involved in the evaluation of this improvement process (see section "IV.D.3.")," to: a) improve text flow in this paragraph and correct the formatting of the parenthetical reference to match that of other such in this document.
970-997	Adds additional text to flesh out this Subsection of the guidance.
99-1001	Changes the sentence, "Manufacturers should always refer to the specific regulations to ensure that they are complying with all regulations," to read, "Manufacturers, processors, and packers should always refer to the specific regulations to ensure that they are complying with all of the CGMP and other regulations that apply to their organization," to: **a)** broaden the guidance to address those firms who process or pack drug products, and **b)** limit the regulations to those that are applicable to their organization
1001-1002	Appropriately corrects the regulatory citations in the "Risk Assessment" row
1006	Changes the word "parts" to "Parts" because that is the proper word case for the citing of a part of the CFR regulations, as is the case here.
1007	Omits the sentence, "Quality professionals are aware that good intentions alone will not ensure good products," because it is an offhand remark that does not add anything of value to this guidance.
1010	Corrects the verb to "has" to from the incorrect verb "have" because the subject of the modifier phrase used here is "each" (number agreement).
1011	Replaces the compound word, "Science-based," with the phrase, "Scientifically sound and appropriate," because the latter ensures that the minimum required by the finished pharmaceutical CGMP regulations is properly reflected in the characteristics of the quality system adopted whereas the draft's "science-based" approaches (e.g., use the USP's test 10 samples from any grab sample of 30 units for uniformity as a batch release sample-evaluation criterion) do not ensure that the approaches used are scientifically sound and appropriate (and the example provided is neither *appropriate* for batches of drug product units *[because it does not meet the CGMP minimum that the samples must be representative of the batch*] nor *scientifically sound* [*because the CGMP regulations require the use of statistical quality control criteria that, based on the applicable recognized international consensus standard, the minimum number that should be tested in the general true process variability known case is on the order of 200 or more representative units from each batch*]).
1015	Inserts the phrase, "and reducing," between the words "assessing" and "risk" to reflect the discussion in the text.
1016-1017	Replaces the phrase, "…product life cycle," with the phrase, "…life of the process and the product it produces," because the alternative wording address the life of both the product and the process while the original only reflects the drug product.
1018-1019	Replaces the phrase, "…analyses of product quality," with the phrase, "…analysis of the quality of incoming and in-process materials and the drug product," because the alternative: a) reflects all of the materials that must have monitoring systems and b0 appropriate corrects the plural word "analyses" to the singular form "analysis," which is the appropriate choice here.
1035	Corrects the improper reference, "*ANSI/ISO/ASQ*," to the correct, "*ANSI/ASQ*," because the standard referred to is "Q9000-2000," which the ANSI/ASQ standard; the corresponding ISO/IEC standard is "9000:2000."
1051	Corrects the improper reference, "*ANSI/ISO/ASQ*," to the correct, "*ANSI/ASQ*," because the standard referred to is "Q9001-2000," which the ANSI/ASQ standard; the corresponding ISO/IEC standard is "9001:2000

Line #	Clarification
1053	Corrects the improper reference, "*ANSI/ISO/ASQ*," to the correct, "*ANSI/ASQ*," because the standard referred to is "Q9004-2000," which the ANSI/ASQ standard; the corresponding ISO/IEC standard is "9004:2000
1055	Corrects the improper reference, "*ANSI/ISO/ASQ* 17025-1999," to the correct, "*ISO/IEC* 17025:1999," because there is no ANSI/ASQ standard and the correct ISO/IEC standard is "17025:1999."
1113-1116	Changes the definition, "**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]," to read, "**CAPA** – "Corrective action and preventive action": A systematic approach that includes procedures needed to: correct ("correction"); prevent recurrence ("corrective action"); and eliminate the cause ("preventive action") of nonconforming product and other quality problems. [Adapted from 21 CFR § 820.100.]," to improve the definition's clarity and grammatical correctness.
1117-1119	Changes the definition, "**Continuous Improvement** – ongoing activities to evaluate and positively change products, processes, and the quality system to increase effectiveness," to read, "**Continuous Improvement** – ongoing activities to evaluate and positively modify products, processes, and quality system to increase process effectiveness and/or enhance product quality," to improve the definition.
1120-1121	Changes the definition, "**Correction** – Repair, rework, or adjustment and relates to the disposition of an existing discrepancy," to read, "**Correction** – Repair, rework, or adjustment relating to the disposition of an existing discrepancy," to improve the definition.
1131-1140	Adds a definition for "**Minimum Process Capability**" to define this not generally understood term.
1151-1152	Changes the definition, "**Quality** – a measure of a product's or service's ability to satisfy the customer's stated or implied needs," to read, "**Quality** – a measure of a product's or a service's conformance to or divergence from the customer's stated or implied needs," to improve the definition.
1153-1155	Changes the definition, "**Quality Assurance** – proactive and retrospective activities that provide confidence that requirements are fulfilled," to read, "**Quality Assurance** – a system that addresses the proactive and retrospective activities that provide confidence that requirements are fulfilled, and the organizational unit with the primary responsibility for overseeing such activities," to improve the definition.
1156-1159	Changes the definition, "**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," to read, "**Quality Control** – 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," to improve the definition.
1160-1161	Changes the definition, "**Quality Management** – accountability for the successful implementation of the quality system," to read, "**Quality Management** – the organization's system for, and the personnel who are accountable for, the successful implementation of the firms' quality system," to improve the definition.
1173-1175	Changes the text here, "In the CGMP regulatory context, the quality system establishes the foundation to promote the effective functioning of the five other major systems," to read, "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," to improve the definition.

Line #	Clarification
1177-1179	Changes the definition, "**Risk Assessment -** A systematic evaluation of the risk of a process by determining what can go wrong (risk identification), how likely is it to occur (risk estimation), and what the consequences are," to read, "**Risk Assessment -** A systematic evaluation of the risk of a process by determining what can go wrong (risk identification), how likely is it to occur (risk estimation), and what the consequences are (risk appraisal)," to improve the definition.
1180-1184	Changes the definition, "**Senior Management** – top management officials in a firm who have the authority and responsibility to mobilize resources," to read, "**Senior Management** – top management officials and/or executive personnel in a 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," to improve the definition.
1187-1191	Adds a definition for "Statistical Quality Control" to define a term that is well understood in industry in general since the 1960's but apparently not generally understood by many in the pharmaceutical industry who are responsible for one or more aspects of the assessment of the quality of drugs, compliance with the applicable CGMP minimums, and/or the assessment of incoming, in-process and drug product substances.