

**Wednesday, 24 November 2004**

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:** 04D-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**Comments On :** “ Draft Guidance for Industry on Quality Systems Approach to  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

Overall, this Draft seems to provide *scientifically sound and appropriate* guidance in most areas.

However, this review found a few areas where the Draft needs to be changed so that it adheres to the *applicable* fundamental scientific and regulatory principles of current good manufacturing practice (CGMP) as outlined in 21 CFR Part 210 and 21 CFR Part 211.

The comments being provided to Docket: "**04D-0443**" are based on a review of "**Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations** [G:\6452dft.doc – 9/28/04 – PDF version].”

The comments speak to elements in the Draft that:

- ❖ *Though required by sound science*, are not mentioned or discussed (e.g., representative inspection [sampling and evaluation]) or
- ❖ Are:
  - inadequately (e.g., the level of quality that conforms to current good manufacturing practice [“Six Sigma”] as opposed to the minimum level of quality required by the CGMP regulations issued in the late 1970’s [95% confidence level at “three sigma”], and the requirement that statistical quality control criteria must be used in the acceptance of each batch for release by the firm’s quality unit),
  - incorrectly (e.g., the requirements for the CGMP-compliant use of a supplier’s report of analysis in lieu of evaluating all of the representative samples taken from each shipment of each lot of a given component), or
  - imprecisely (e.g., the requirements for the CGMP-compliant in-process controls)  
addressed.

To aid those who will review them, the current “News Gothic MT” font is used and the text is indented on both margins when a rationale or justification is provided.

When a wording change within existing wording is suggested, the comment text is in *italicized News Gothic MT* or, when the existing text is *italicized*, in a normal News Gothic MT font.

In general, the original text is quoted (“original text”) in a “Times New Roman” font and quoted references to CGMP and other FDA-recognized documents are presented in a “Lydian” font.

Should anyone in the Agency who reviews said comments need clarification on a given suggestion or take issue with what has been stated, then they should e-mail (**drking at dr-king.com**) their observation and the scientifically sound rationale that supports their remarks and, where possible, I will provide appropriate clarifying remarks or an answer to their observations.

Respectfully submitted,

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2  
3 **1.** Change Lines 18 to 32 to read:

4 “FDA's guidance documents, including this draft guidance, do not establish legally enforceable  
5 responsibilities. Instead, guidances describe the agency's current thinking on a topic and should  
6 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
7 cited. The use of the word *should* in agency guidances means that something is suggested or  
8 recommended, but not required. The use of the words *can* or *may* or derivatives thereof  
9 (i.e., *could* or *might*) in agency guidances means that alternatives are suggested  
10 or recommended, but not required. The use of the word *must* in agency  
11 guidances means that something is required by a specific statute or regulation  
12 (e.g., samples *must* be *representative* of the population [*lot* or *batch*] to satisfy 21  
13 CFR Sec. 211.160(b)).”  
14

15 Since each guidance is, in general, a stand-alone document, the agency  
16 should define the import of the words *may*, *can*, and *must* whenever the  
17 agency sees the need to define the import of the word *should*.  
18

19 **2.** Change Lines 78 to 83 to read:

20 “The overarching philosophy articulated in both the CGMP regulations *and* in robust modern  
21 quality systems is:  
22  
23

24 ***Quality must be built into the product, the critical variable characteristics for ALL***  
25 ***inputs must be adequately controlled, and, though required by CGMP,***  
26 ***representative-sample testing alone cannot be relied on to ensure product quality.***  
27

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

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

34 Finally, *unless population-representative samples are tested*, a  
35 manufacturer **cannot** validly assess the quality of lots or batches of finished  
36 products that the firm makes.

37 Thus, the text should be revised as suggested if, *as they should be*, the  
38 fundamental premises are to be aligned with the quality ***minimums*** set  
39 forth in the CGMP regulations.  
40

41 **3.** Change Lines 92 to 97 to read:

42 “● It is important that we harmonize the CGMP *regulations* to the extent possible with other  
43 widely used quality management systems including ISO 9000, non-U.S. pharmaceutical  
44 quality management requirements, and FDA’s own medical device quality system  
45 regulations. With the globalization of pharmaceutical manufacturing and the increasing  
46 prevalence of drug- and biologic-device combination products, the convergence of quality  
47 management principles across different regions and among various product types is very  
48 desirable provided *the current CGMP minimums are met.*”  
49  
50

51 The acronym “CGMPs” is not defined and should, therefore, not be used  
52 when the topic is clearly the *CGMP regulations*. [Note: 21 CFR Part 26,  
53 “MUTUAL RECOGNITION OF PHARMACEUTICAL GOOD MANUFACTURING  
54 PRACTICE REPORTS, MEDICAL DEVICE QUALITY SYSTEM AUDIT REPORTS, AND  
55 CERTAIN MEDICAL DEVICE PRODUCT EVALUATION REPORTS: UNITED STATES  
56 AND THE EUROPEAN COMMUNITY,” does define a similar acronym, “GMP’s,” for  
57 the phrase “good manufacturing practices” in 21 CFR Sec. 26.1(c). Based on the  
58 preceding, the “appropriate” acronym, if any, would be “CGMP’s.” However, this  
59 commenter believes that the phrase “CGMP regulations” should be used because:  
60 a) that is the topic being discussed and b) CGMP is clearly an adjective  
61 delineating the regulations that this guidance is intended to subsume.]

62 The *required goal*, of meeting all CGMP *minimums*, needs to be explicitly  
63 stated because most quality systems are **not** goal directed.

64 Moreover, *in this commenter’s experience*, many of the product quality  
65 problems that this commenter sees are caused by the inadvertent or, *more*  
66 *commonly*, deliberate failure of the manufacturer to comply with one or  
67 more of the clear requirement *minimums* set forth in the CGMP regulations.  
68

69 **4.** Change Lines 115 to 116 to read:

71 “Drug Evaluation and Research (CDER), and the Center for Veterinary Medicine (CVM). It  
72 may also be useful to manufacturers of *the* components used in the manufacture of these  
73 products.”  
74

75 The addition of the word *the* Improves the readability of the statement  
76 made.  
77

78 **5.** Change Lines 154 to 157 to read:

80 “Every pharmaceutical product has established identity, strength, purity, and other quality  
81 characteristics designed to ensure the required levels of safety and effectiveness. For the  
82 purposes of this draft guidance document, the phrase *achieving quality* means achieving these  
83 characteristics for *all* the product *units*.”  
84

85 *Since, in general, the quality expectations for drugs are higher than those for*  
86 *most other goods*, it is important that each of the *units* in each *batch* or *lot* of  
87 product be ensured of meeting its established identity, strength, purity,  
88 and other quality characteristics to ensure that the unit or units  
89 administered to each patient should meet each and every one of these  
90 quality criteria at release and, *provided they have been properly handled after*  
91 *release*, are assured of being both safe and effective.

92 This is especially critical when the patient only receives one or a few (<  
93 10 units) in a given treatment regimen.  
94

95 **6.** Change Lines 161 to 165 to read:

97 “*Quality by design* means designing and developing manufacturing processes *during the product*  
98 *development* stage to consistently ensure ~~each~~ *each unit produced meets all of its predefined*

99 quality *criteria* at the end of the manufacturing process.<sup>5</sup> A quality system provides a sound  
100 framework for the transfer of process knowledge from development to the commercial  
101 manufacturing processes and for post-development changes and optimization.”  
102

103 Again, the proper quality system’s goal for a pharmaceutical  
104 manufacturer should be to ensure that every unit, **not just those evaluated**,  
105 in each batch will, *if tested*, meet all of their predetermined *scientifically*  
106 *sound and appropriate* quality criteria.  
107

108 7. Change Lines 169 to 173 to read:

110 “The concept *risk management* is a major focus of the ‘Pharmaceutical CGMPs for the 21<sup>st</sup>  
111 Century Initiative.’ Risk management can guide the setting of specifications and process  
112 parameters. Risk assessment is also used in determining the need for discrepancy investigations  
113 and corrective action. ~~As~~ *When* risk assessment<sup>6</sup> is used more formally by manufacturers, it ~~can~~  
114 *should* be implemented within ~~the~~ a quality system framework. *It should be noted that the*  
115 *CGMP regulations for finished pharmaceuticals (21 CFR Part 211) establish risked-*  
116 *based minimums for components, process, in-process materials, and drug-product*  
117 *quality assessment for acceptability for release that, given their timeframe and wording,*  
118 *set a minimum level of confidence that is **not less than 95%** – a level of quality that is*  
119 *well below today’s recognized ‘de facto’ standards of performance for quality*  
120 *excellence (‘Six Sigma’).”*  
121

122 The wording changes suggested are designed to guide the reader to an  
123 understanding that, *when used*, risk assessment should be incorporated  
124 into the foundation of the quality system framework used.

125 The commenter’s added statement is provided to ensure that all parties  
126 clearly understand that the CGMP regulations for finished pharmaceuticals  
127 clearly establish risk-based quality *minimums* for each batch of drug  
128 product that, *based on their timeframe and wording*, set a 95%-confidence-  
129 level floor (*minimum*) (with acceptable quality levels for predicted out-of-  
130 specification units between 0.1 % and 1+ %) for each “batch” quality  
131 characteristic that a given drug product is required to meet at release  
132 before the batch can be accepted (as per 21 CFR Sec. 211.165(d)).

133 In addition, that added statement properly places the CGMP  
134 regulations’ quality *minimums* below today’s current “de facto” “Six Sigma”  
135 quality expectations.  
136

137 8. Insert after line 174:

#### 139 **D. Quality Control**

140

141 Inherent in all quality management systems is the need to control the quality of  
142 the outcomes by exerting various defined levels of direct and indirect control on  
143 the inputs, processes, procedures, and processors that produce the desired

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

<sup>6</sup> This concept is being developed under the ICH Q9 Risk Analysis Expert Working Group.

outcomes. In pharmaceutical manufacturing, quality control is the umbrella term

**FIGURE 1 Overview Of The Mandated Controls Structure**

[Starting At 21 CFR 211.160 – General requirements]

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**21 CFR 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.



**21 CFR 211.160(b)**

Laboratory controls shall include the establishment of *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. Laboratory controls shall include:

- (1) Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
- (2) Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.
- (3) Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.
- (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

211.170  
*Reserve  
samples*

211.173  
*Laboratory  
animals*



**Subpart E**  
**Control of**  
**Components And**  
**Containers And**  
**Closures**

**Subpart F**  
**Production &**  
**Process**  
**Controls**

*Subpart G*  
*Packaging &*  
*Labeling Control*

**211.165 Testing and release for distribution**  
*211.166 Stability testing requirements*  
*211.167 Special testing requirements*  
*211.176 Penicillin contamination*

*(Not Discussed)*

*(§§ 211.166, 211.167, and 211.176 were not discussed)*

180 used to encompass all aspects of a quality system, which innately control the  
181 degree to which the process outcomes (in-process materials and products)  
182 *minimally* meet, or *ideally* exceed, their expectations. When examined from the  
183 viewpoint of quality control or, simply, control, it is obvious that the CGMP  
184 regulations for finished pharmaceuticals (21 CFR Part 211) are control centric.  
185 Thus, the “quality control” organizational structure of the CGMP regulations for  
186 finished pharmaceuticals is that shown in **Figure 1**. The umbrella regulations  
187 that encompass all of the “internal quality controls” governing the firms finished  
188 pharmaceutical operations are contained in 21 CFR Sec. 211.160. Thus, when  
189 considered from a logical “control flow” viewpoint, it becomes clear that the  
190 fundamental bases (foundation) for all of the manufacturer’s controls reside in 21  
191 CFR Sec. 211.160, a section that is simply titled “**General requirements.**”  
192

193 **9.** Change Line 175 to read:

194  
195 **“E. CAPA (Corrective *Action* and Preventive Action)”**  
196

197 The letter was change to reflect the change imposed by inserting  
198 another section above this one and the word “**Action**” added after the word  
199 “Corrective” to make the interpretative text in the header match the acronym  
200 “CAPA.”  
201

202 **10.** Change Lines 185 to 191 to read:

203  
204 **“F. Change Control**  
205

206 *Change control* is another well-known CGMP regulatory concept that focuses on managing  
207 change to prevent unintended consequences. *Ideally, change control should be incorporated*  
208 *into the “Maintenance Qualification” phase of the ongoing life-cycle approach to*  
209 *maintaining a process in a validated (“proven valid”) state.* The major implementation of  
210 change control in the CGMP regulations is ~~through~~ *expressed in the responsibilities*  
211 *assigned of the quality control unit. In addition, certain manufacturing changes (e.g., changes*  
212 *that alter specifications, a critical product attribute or bioavailability) require regulatory filings*  
213 *and prior regulatory approval (601.12 and 314.70).”*  
214

215 Since this guidance recognizes the importance (**see**, for example,  
216 Draft’s Lines 105 and 658) of the life-cycle approach to the development  
217 and maintenance of the quality of a drug product and states, “the entire life-  
218 cycle should be addressed by the establishment of continuous improvement mechanisms  
219 in the quality system. Thus, in accordance with the quality systems approach, process  
220 validation is not a one time event, but an activity that continues,” the ideal would be  
221 that an on-going journey-based approach to the life cycle of each product  
222 should be adopted.

223 In such ideal instances, the life cycle of a product would be defined in a  
224 set of qualification phases that begin with design/development  
225 qualification and proceed to “Maintenance Qualification” (“MQ”) at the  
226 point that the FDA accepts the manufacturer’s systems for consistently  
227 manufacturing acceptable product and ends with “Closure Qualification”  
228 (“CQ”) when the manufacturer either stops making a given product or

229 switches to a different manufacturing process for that product and receives  
230 FDA acceptance for that different process.

231 The other changes suggested simply improve the accuracy of the  
232 statement made in the first instance and the readability of the draft  
233 guidance in the second case.  
234

235 **11.** Change Lines 193 to 198 to read:

237 “A quality system also contains change control activities, including quality planning and control  
238 of revisions to specifications, process parameters, and procedures. In this guidance, *change* is  
239 discussed in terms of creating a regulatory environment that encourages change towards  
240 continuous improvement *in the quality of the process, without adversely affecting in-*  
241 *process quality, or the quality of the product.* This means a manufacturer is empowered to  
242 make changes ~~based on~~ that reduce the variability of materials used in manufacturing and  
243 otherwise optimization of the process ~~from learning over time~~ based on the ongoing use of  
244 statistical control techniques that permit the manufacture to separate the effect of  
245 critical characteristic variation from random outcome fluctuation.”  
246

247 In the first instance, the added phrase “*in the quality of ...*” is added to  
248 point out that the goal of CGMP-compliant improvement should be to  
249 improve the quality of the process without adversely affecting product  
250 quality or, better, to improve the quality of the product.

251 The current regulatory environment with its “AR,” “CBE-0,” “CBE-30,”  
252 “supplement required,” and “compatibility protocol” options already  
253 provide the flexibility needed for changes.

254 However, *in practice*, often the changes made not only do **not** improve  
255 product quality but also have the effect of actually reducing one or more of  
256 the critical quality characteristics of the product.

257 This guidance should make it clear that a quality system’s approach  
258 does **not** permit any change that reduces any aspect of quality of the  
259 product.

260 In the second instance, this guidance needs to make it crystal clear that  
261 statistical control tracking and trending techniques should be used in any  
262 quality system’s approach that is applicable to pharmaceutical  
263 manufacturing.  
264

265 **12.** Change Lines 200 to 212 to read:

267 “ **G. The Quality Unit**

268  
269 Many of the modern quality systems ideas described in this section correlate very closely with  
270 the CGMP regulations (refer to the charts later in the document). Current industry practice  
271 generally divides the responsibilities of the Quality Control Unit (QCU), as defined in the CGMP  
272 regulations, ~~between~~ among the quality control (QC), ~~and~~ quality assurance (QA) and  
273 regulatory affairs (RA) functions.  
274

- 275 • QC usually consists of assessing the suitability ~~testing~~ of incoming components,  
276 containers, closures and labeling, ~~selected~~ critical in-process materials and the  
277 finished products to evaluate the performance of the manufacturing process, ~~and~~ to

278 ensure adherence to proper specifications and limits, *and determine the acceptability*  
279 *of each batch for release.*

280 • QA primarily includes the review and approval of all procedures related to production,  
281 maintenance, and review of associated records, and auditing, and performing trend  
282 analyses.

283 • *RA typically acts as the quality function's bi-directional interface between the*  
284 *other quality functions and the FDA."*  
285

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

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

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

304 This is the case because RA typically oversees the conduct of agency  
305 inspections, files all submission documents and annual reports, and  
306 addresses all issues that arise with the agency.  
307

308 **13.** Change Lines 213 to 220 to read:

309 "This guidance uses the term *quality unit*<sup>7</sup> (QU) to reflect modern practice while remaining  
310 consistent with the CGMP definition in 21 CFR Sec. 210.3(b)(15). The concept *quality unit* is  
311 also consistent with modern quality systems in ensuring that the various operations associated  
312 with all systems are *scientifically sound, appropriate, appropriately implemented and*  
313 *conducted, approved, modified and monitored.* The CGMP regulations specifically assign the  
314 quality unit the authority to create, monitor, *approve, modify,* and implement the quality  
315 system. However, the quality unit is not meant to take on the responsibilities of other units of a  
316 manufacturer's organization, such as the responsibilities handled by manufacturing personnel,  
317 engineers, and development scientists.<sup>8</sup>"  
318  
319

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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.

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

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

323 The other changes suggested by this commenter are intended to  
324 recognize that implementation, approval and modification of the quality  
325 system.  
326

327 **14.** Change Lines 222 to 238 to read:  
328

329 “Other CGMP assigned responsibilities of the quality unit are consistent with a modern quality  
330 system approaches (see § 211.22):  
331

- 332 • *Ensuring the controls are scientifically sound and appropriate as well as*  
333 *ensuring that the samples sampled and the samples evaluated are*  
334 *representative of the population (batch or lot) from which they are taken.*
- 335 • Ensuring that controls are implemented and completed satisfactorily during  
336 manufacturing operations
- 337 • Ensuring that developed procedures and specifications are appropriate and followed,  
338 including those used by a firm under contract to the manufacturer
- 339 • Approving or rejecting *incoming and in-process materials*, and drug products —  
340 although such activities do not substitute for, or preclude, the daily responsibility of  
341 manufacturing personnel to build quality into the product
- 342 • Reviewing production records and *overseeing the investigations* of any unexplained  
343 discrepancies

344 Under a robust quality system, the *product and process development units*, manufacturing  
345 units, and the quality unit can remain independent, but still be included in the total concept of  
346 producing quality products. In very small operations, a single individual can function as the  
347 quality unit. That person is still accountable for implementing all the controls and reviewing  
348 results of manufacture to ensure that product quality standards have been met.”  
349

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

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

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

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

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

372 The suggested change in the last bullet recognizes that the quality unit  
373 should appropriately oversee the conduct of any production discrepancy  
374 investigations because the production unit that generated the discrepancy  
375 is usually better equipped to conduct the investigation than the quality unit  
376 *per se*. [Note: In this context, the laboratories reporting to the quality unit are a  
377 production unit – **they produce test results**.]

378 The need to explicitly include the “*product and process development units*”  
379 in the list of units outlined in a “robust quality system” stems from the reality  
380 that building quality into a product must begin with those who interactively  
381 develop both the product and the process for its manufacture.  
382

383 **15.** Change Line 239 to read:

384 “**H. Six-system Inspection Model**”

385 This change aligns this subsection’s letter with the revised text.  
386  
387  
388

389 **16.** Change Line 255 to read:

390 “**FIG. 2- SIX-SYSTEM INSPECTION APPROACH**”

391 The Figure “number is change to reflect the figure added earlier in the  
392 text by this commenter.  
393  
394  
395

396 **17.** Change Lines 276 to 280 to read:

397 “The goal of this section is to describe a model for use in pharmaceutical manufacturing that can  
398 help achieve compliance with CGMP regulations. It should be noted that implementing an  
399 effective quality system in a manufacturing organization ~~will~~ may require significant costs in  
400 time and resources. However, the long-term benefits of implementing a quality system ~~will~~  
401 *should* outweigh the costs.<sup>10</sup>”  
402  
403

404 This commenter suggest the first change because, *in this commenter’s*  
405 *experience*, there have been times that implementing an effective quality  
406 has actually reduced the existing costs in time and resources.

407 This has been the case because the costs incurred were more than  
408 offset by the time and resource savings from reducing process waste,  
409 investigations and investigation time, product loss, and batch or lot  
410 rejection.

411 This commenter suggests the second change because guidance “*should*”  
412 only speculate about the expected outcomes of the changes proposed and  
413 **not** about what “will” happen.

---

<sup>10</sup> See Reference #3

414 This commenter has seen instances where poorly implemented quality  
415 systems produced no long-term benefits and did significantly increase  
416 costs.

417 In most of these instances, the manufacturer’s “comprehensive” quality  
418 system failed to encompass product/process development or, *when*  
419 *product/process development was addressed*, did **not** adequately control the  
420 quality of the incoming components used in the manufacturing process.  
421

422 **18.** Change Lines 276 to 280 to read:

423  
424 “This section describes a robust quality systems model, which, if *properly* implemented, can  
425 provide the controls needed to consistently produce a product of *more than* acceptable quality.”  
426

427 The first change recognizes the reality that proper implementation is a  
428 critical component if the manufacturer is to meet expected outcomes.

429 Many of the recent major product failures can be traced to improperly  
430 implemented quality systems.

431 In the second instance, the goal must be processes that consistently  
432 produce **more than** acceptable quality to ensure that, *when the worst-case*  
433 *variabilities occur*, the product produced should still be acceptable.

434 *For processes that vary*, those who set their target at merely producing  
435 acceptable product are tolerating the fact that such processes do produce  
436 some fraction of unacceptable product units.

437 *In a robust quality system*, the target for product quality should be set  
438 sufficiently higher than the least acceptable quality by an amount sufficient  
439 to ensure that, with a high level of confidence (95 % or higher), the  
440 probability of producing a product with unacceptable quality is less than  
441 one in some multiple (usually, 3 or higher) of the quantity of product  
442 produced in any given period (typically, a year). [**Note:** For batch processes,  
443 *if a manufacturer produces 120 batches a year*, then a properly implemented robust  
444 quality system should ensure that the manufacturer can be at least 95% confident  
445 that the probability of an unacceptable batch being produced is less than 1 in  
446 360.]  
447

448 **19.** Change Lines 343 to 344 to read:

449  
450 “Managers have the responsibility to communicate employee roles, responsibilities, and  
451 authorities within the system and ensure that interactions are defined and understood.  
452 *Managers are also responsible for ensuring that the documented procedures match*  
453 *actual practice and that all who report to them are properly trained and follow all*  
454 *applicable procedures.*”  
455

456 Based on this commenter’s experience, *beyond communicating to the*  
457 *employees and ensuring that interactions are defined and understood*,  
458 managers should also have the additional responsibilities outlined above.  
459

460 **20.** Change Lines 353 to 365 to read:

461  
462 “Implementing a robust quality system can help ensure compliance with regulations related to  
463 safety, identity, strength, quality, and purity as long as the quality system ~~addresses~~ *meets or*

464 exceeds the *requirement minimums* of CGMP regulations as well as *meets* the needs of the  
465 manufacturer. Under the quality systems model, the Agency recommends that senior managers  
466 ensure that the quality system they design and implement provides clear organizational guidance  
467 and facilitates systematic evaluation of issues. For example, according to the model, when  
468 documenting a quality system, the following should be included.  
469

- 470 • The scope of the quality system, including any outsourcing (see IV.B.4.)
- 471 • The standard of quality that will be used
- 472 • The manufacturer’s policies to implement the quality systems criteria, and the  
473 supporting objectives (see IV.A.4.)
- 474 • The procedures needed to establish and maintain the quality system
- 475 • *The proofs that establish that the quality system meets the requirement*  
476 *minimums of the applicable CGMP regulations.”*  
477

478 To be CGMP compliant, a quality system must meet or exceed all of the  
479 applicable CGMP *minimums* (see 21 CFR Sec.210.1 and 21 CFR Sec.  
480 211.1(a), “a) The regulations in this part contain the minimum current good manufacturing  
481 practice for preparation of drug products for administration to humans or animals.”).

482 *Since the CGMP regulations at 21 CFR Sec 211.160(a) explicitly state,*  
483 *“The establishment of any specifications, standards, sampling plans, test procedures, or other*  
484 *laboratory control mechanisms required by this subpart, including any change in such*  
485 *specifications, standards, sampling plans, test procedures, or other laboratory control*  
486 *mechanisms, shall be drafted by the appropriate organizational unit and reviewed and*  
487 *approved by the quality control unit,” and inherent in “establishing” any control is*  
488 *the element of proof, the manufacturer must have proof that establishes the*  
489 *validity of said controls (including the quality system itself).*

490 Moreover, because all “laboratory” controls, and, by inference, all other  
491 controls are required (21 CFR Sec. 211.160(b)) to be proven to be  
492 (established) “scientifically sound and appropriate specifications, standards, sampling  
493 plans, and test procedures designed to assure that components, drug product containers,  
494 closures, in-process materials, labeling, and drug products conform to appropriate standards of  
495 identity, strength, quality, and purity,” and 21 CFR Sec. 110 (“Sampling and testing of  
496 in-process materials and drug products.

497 (a) To assure batch uniformity and integrity of drug products, written procedures shall be  
498 established and followed that describe the in-process controls, and tests, or examinations to  
499 be conducted on appropriate samples of in-process materials of each batch. Such control  
500 procedures shall be established to monitor the output and to validate the performance of  
501 those manufacturing processes that may be responsible for causing variability in the  
502 characteristics of in-process material and the drug product. Such control procedures shall  
503 include, but are not limited to, the following, where appropriate:

- 504 (1) Tablet or capsule weight variation;
- 505 (2) Disintegration time;
- 506 (3) Adequacy of mixing to assure uniformity and homogeneity;
- 507 (4) Dissolution time and rate;
- 508 (5) Clarity, completeness, or pH of solutions.

509 (b) Valid in-process specifications for such characteristics shall be consistent with drug product  
510 final specifications and shall be derived from previous acceptable process average and  
511 process variability estimates where possible and determined by the application of suitable  
512 statistical procedures where appropriate. Examination and testing of samples shall assure  
513 that the drug product and in-process material conform to specifications.

514 (c) In-process materials shall be tested for identity, strength, quality, and purity as  
515 appropriate, and approved or rejected by the quality control unit, during the production  
516 process, e.g., at commencement or completion of significant phases or after storage for  
517 long periods.

518 (d) Rejected in-process materials shall be identified and controlled under a quarantine system  
519 designed to prevent their use in manufacturing or processing operations for which they are  
520 unsuitable.”)

521 these proofs must cover **all** aspects of manufacturing.

522 Moreover, this commenter consistently finds that the lack of any proof  
523 that a given practice is *scientifically sound* is a clear indication that the  
524 practices in use probably are **not** *scientifically sound*, much less *appropriate*.

525 Further, *whenever possible*, the manufacturer must use recognized  
526 consensus standards, where such exist, and/or appropriate *population*  
527 *statistics*

528 Examples of current problem practices that pervade the pharmaceutical  
529 industry include the ongoing scientifically unsound use of:

530  
531 1. a “1 plus square root of n” sampling plan for non-discrete materials  
532 packed in drums and bags,  
533

534 2. the USP’s IDENTIFICATION tests, which are **not** generally *identity tests*  
535 much less *specific identity tests*, instead of the required “**identity test**” (21  
536 CFR Sec. 211.84(d)(1)) or “**specific identity test**” required when the  
537 component manufacturer’s “**report of analysis**” is used instead of the drug  
538 manufacturer’s testing the requisite samples.  
539

540 3. the ROA (COA) or lab’s assay value without correction for its typical  
541 “2%” uncertainty instead of, *as the manufacturer should*, the use of the  
542 “as is,” “weight percent” *minimum* purity to calculate the amount of  
543 each active pharmaceutical ingredient to add to a formulation to meet  
544 the clear requirement formulation requirement minimum set forth in 21  
545 CFR Sec 211.101(a), “The batch shall be formulated with the intent to provide not  
546 less than 100 percent of the labeled or established amount of active ingredient.”  
547

548 4. the use other than *valid population statistics* to establish valid in-process  
549 specifications (21 CFR Sec. 211.110(b), “Valid in-process specifications for such  
550 characteristics shall be consistent with drug product final specifications and shall be derived  
551 from previous acceptable process average and process variability estimates where possible  
552 and determined by the application of suitable statistical procedures where appropriate.  
553 Examination and testing of samples shall assure that the drug product and in-process  
554 material conform to specifications.”  
555

556 5. procedures that fail to take and test *batch-* or *lot-* *representative samples*  
557 as required in 21 CFR Sec. 211.160(b) [italicization used for emphasis],  
558 “Laboratory controls shall include the establishment of scientifically sound and appropriate  
559 specifications, standards, sampling plans, and test procedures designed to assure that  
560 components, drug product containers, closures, in-process materials, labeling, and drug  
561 products conform to appropriate standards of identity, strength, quality, and purity.  
562 Laboratory controls shall include:

563 (1) Determination of conformance to appropriate written specifications for the acceptance  
564 of each lot within each shipment of components, drug product containers, closures, and  
565 labeling used in the manufacture, processing, packing, or holding of drug products.  
566 The specifications shall include a description of the sampling and testing procedures  
567 used. *Samples shall be representative* and adequately identified. Such procedures shall  
568 also require appropriate retesting of any component, drug product container, or  
569 closure that is subject to deterioration.

570 (2) Determination of conformance to written specifications and a description of sampling  
571 and testing procedures for in-process materials. Such *samples shall be representative*  
572 and properly identified.

573 (3) Determination of conformance to written descriptions of sampling procedures and  
574 appropriate specifications for drug products. Such *samples shall be representative* and  
575 properly identified.

576 (4) The calibration of instruments, apparatus, gauges, and recording devices at suitable  
577 intervals in accordance with an established written program containing specific  
578 directions, schedules, limits for accuracy and precision, and provisions for remedial  
579 action in the event accuracy and/or precision limits are not met. Instruments,  
580 apparatus, gauges, and recording devices not meeting established specifications shall  
581 not be used.”

582  
583 6. the USP’s “in commerce, grab sample” control criteria, which are **not**  
584 based on a *statistical sampling plan* and are **not**, therefore, appropriate for  
585 batch or lot release for distribution, to release batches of drugs instead of  
586 using the CGMP-required *statistical quality control criteria* to accept each  
587 batch for release (21 CFR Sec. 211.165(d), “Acceptance criteria for the sampling  
588 and testing conducted by the quality control unit shall be adequate to assure that batches of  
589 drug products meet each appropriate specification and appropriate statistical quality control  
590 criteria as a condition for their approval and release. The statistical quality control criteria  
591 shall include appropriate acceptance levels and/or appropriate rejection levels.”).

592  
593 **21.** Change Lines 366 to 374 to read:

594  
595 “It is recommended under a modern quality systems approach that a formal process be  
596 established to submit change requests to directives. It is also recommended that, when operating  
597 under a quality system, manufacturers develop and document record control procedures to  
598 complete, secure, protect, and archive records, including data, which act as evidence of  
599 operational and quality system activities. This approach is consistent with the CGMP  
600 regulations, which require manufacturers to ~~develop and document~~ *establish and follow*  
601 *scientifically sound and appropriate written* controls for specifications, plans, and  
602 procedures (21 CFR Sec. 211.160) that direct operational and quality system activities and to

603 ensure that these directives are accurate, appropriately reviewed and approved, and available for  
604 use (see the CGMP regulations at §§ 211.22 (c) and (d)).”  
605

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

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

610 Finally, the process controls’ requirement *minimum* “*and followed*” also  
611 occurs in Sections 211.80(a), 211.100 (b), 211.110(a), 211.113(a) and  
612 (b), 122(a), 125(f), 130, 142, 150, 165(c), 166(a), and 167(a), (b), and (c).  
613

614 **22.** Change Lines 406 to 417 to read:

615 “provided). Under a quality system, the review should consider at least the following:

- 616 • The appropriateness of the quality policy and objectives
- 617 • The results of audits and other assessments
- 618 • Customer feedback, including complaints
- 619 • The analysis of data trending results
- 620 • The status of actions to prevent a potential problem or ~~the~~ *recurrence of previous*  
621 *problems*
- 622 • *The status of any follow-up actions from previous management reviews*
- 623 • Any changes in business practices or environment that may affect the quality system  
624 (such as the volume or type of operations)
- 625 • Product characteristics meet *both the CGMP minimums and the customer’s needs*”  
626

627 In general, the first two suggestions are intended to improve the clarity  
628 and accuracy of the statements modified.

629 The third change reflects the reality that, regardless of the customer’s  
630 needs, a pharmaceutical manufacturer is a *regulated* business that must  
631 meet, or exceed, all of the applicable requirement *minimums* set forth in  
632 the CGMP regulations.  
633  
634

635 **23.** Change Lines 406 to 417 to read:

636 “Under a quality system, the results of a management review ~~are expected to~~ *must* be recorded.  
637 Planned actions should be implemented using effective corrective and preventive action and  
638 change control procedures.”  
639

640 This commenter knows that the word “*must*” should be used here  
641 instead to the draft’s convoluted “*are expected to*” – an “*expected*” action is  
642 an action that is required for conformance – therefore, it is a “*must*.”  
643  
644

645 **24.** After Line 431, insert the following text:

646 6. *Audit Operations to Ensure Compliance*  
647  
648

649 Though often overlooked, system audit is a key component of any robust quality  
 650 system. Management is responsible for not only auditing all operations to ensure  
 651 that all controls are being adhered to but also for ensuring that all personnel are  
 652 properly trained and procedure compliant. In their capacity as self auditors, all  
 653 personnel are responsible for operating in conformance to systems’  
 654 documentation as well as identifying and reporting any gaps or deficiencies in the  
 655 existing systems’ documentation or any areas where the existing procedures need  
 656 to be or can be improved. In their capacity as peers, all personnel are  
 657 responsible for auditing their peers’ compliance to all the applicable  
 658 requirements of the manufacturer’s quality system. For manufacturers registered  
 659 to some recognized quality standard, the registering firm’s auditors are also  
 660 responsible for auditing the registered manufacturer’s adherence to the  
 661 recognized Quality System standard as well as all the requirements of the  
 662 manufacturer’s quality system.

664 Inherent to all quality systems is a need (requirement) that the  
 665 manufacturer claiming to comply with a given quality system must include  
 666 an audit function in the system.

667 Unlike review, which is a retrospective examination, audit is a proactive  
 668 checking of the manufacturer’s operational systems for adherence to all  
 669 aspects of the firm’s documented quality system.

670 Under CGMP, the quality system audit function encompasses audits by  
 671 self, peers, managers, and outside parties, including the agency.

672 **25. Change Table following Line 435 to read:**

<b>21 CFR CGMP Regulations Related to Management Responsibilities</b>	
<b>Quality System Element</b>	<b>Regulatory Citations</b>
1. Leadership	—
2. Structure	Establish quality function: § 211.22 (a) (see definition § 210.3(b)(15))
	Notification: § 211.180(f)
3. Build QS	QU procedures: § 211.22(d)
	QU procedures, specifications: § 211.22(c), with reinforcement in: §§ 211.100(a), and 211.160(a)
	QU control steps: § 211.22(a), with reinforcement in §§: 211.42(c), 211.84(a), 211.87, 211.101(c)(1), 211.110(c), 211.115(b), 211.142, 211.165(d), and 211.192
	QU quality assurance; review/investigate: § 211.22(a), 211.100(a-b) 211.180(f), 211.192, and 211.198(a)
	Record control: § 211.180(a-d), 211.180(c), 211.180(d), 211.180(e), 211.186, 211.192, 211.194, and 211.198(b)
4. Establish Policies, Objectives and Plans	Procedures: § 211.22(c-d), 211.100(a)
5. System Review	Record review: § 211.180(e), <del>211.192</del> , and 211.198(b)(2)
6. System Audit	Record review: § 211.160(a), 211.180(e), 211.184(d), 211.192, 211.194(a)(8), and 211.198(b)(2)

675

676 Changes in this Table were made to improve grammar and align Table  
677 with changes in the text that added a “System Audit” section.  
678

679 **26.** Change Lines 447 to 456 to read:

681 “Under a robust quality system, there should be sufficient allocation of resources for quality  
682 system and operational activities. Under the model, senior management, or a designee, is  
683 responsible for providing adequate resources for the following:  
684

- 685 • To supply and maintain the appropriate facilities and equipment to consistently  
686 manufacture a quality product *in compliance with CGMP* (see §§ 211 Subparts C &  
687 D)
- 688 • To acquire and receive materials, *including labeling*, that *meet or exceed their*  
689 *applicable established CGMP minimums and are suitable for their intended purpose*  
690 (see §§ 211 Subpart E & 211.122)
- 691 • For processing the materials *in a CGMP-compliant manner* to produce the finished  
692 drug product (see §§ 211 Subpart F)
- 693 • *For packaging and labeling the finished drug product into finished packaged*  
694 *drug product* (see §§ 211.125, 130, 132, 134, 137 and 160(b)(1))
- 695 • For the *CGMP-compliant* laboratory analysis of *incoming* (see §§ 211.84(d), 87,  
696 94(d), and 122(a)) and *in-process materials* (see §§ 211.110 and 160(b)(2))  
697 and the finished drug product (see §§ 211.160(b)(3), 165, 166 and 167),  
698 including *the collection, storage, and examination of representative incoming*  
699 *material* (see §§ 211.160(b)(1)), *in-process* (see §§ 211.160(b)(2)), *stability*  
700 (see §§ 211.160(b)(3) and 166), and *reserve samples* (see § 211.170)
- 701 • *For the CGMP-compliant acceptance or rejection of each batch or lot of drug*  
702 *product for release for distribution* (see § 211.165) *using representative sample*  
703 *evaluations* (see § 211.160(b)(3)) and *statistical quality control* (see §  
704 211.165(d))

705 The changes made have been introduced to better align the text with the  
706 clear CGMP requirement minimums and provide suitable references for  
707 each item in the bulleted items.

708 The added bullet is included because this is one quality system’s  
709 “CGMP requirement *minimum*” area that many manufacturers have simply  
710 ignored and the agency has repeatedly refused to take the requisite  
711 corrective actions to bring these manufacturers into compliance.  
712

713 **27.** Change Lines 502 to 507 to read:

715 “According to the CGMP regulations, equipment must be qualified, calibrated, cleaned, and  
716 maintained to prevent contamination and mix-ups (§§ 211.63, 211.67, and 211.68). [~~Note: that~~  
717 The CGMP regulations require a higher standard for calibration and maintenance than most generic  
718 quality system models.] The CGMP regulations place as much emphasis on process equipment as  
719 on testing equipment (§ 211.42(b)), while ~~most~~ *the majority of quality systems focus only on*

720 testing equipment.<sup>12</sup> However, the quality system in ISO/IEC 17025:1999, though titled,  
721 ‘General Requirements for the Competence of Testing and Calibration Laboratories,’  
722 (Reference 14) provides a general quality system that matches the needs of a  
723 pharmaceutical manufacturing operation in which controls, evaluations, and numerical  
724 values are critical aspects of the system. It applies to any organization that wants to  
725 assure its customers of precision, accuracy and repeatability of results produced.  
726 Moreover, ISO/IEC 17025 explicitly addresses facilities and equipment, calibration  
727 and maintenance, and all aspects of control and measurement unlike most other quality  
728 systems.”  
729

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

732 The added statements are offered because they provide an “out of the  
733 box” approach to an ISO-9000-related quality system, ISO/IEC 17025, that  
734 does seem to be a good match to the needs of a CGMP-compliant quality  
735 system.  
736

737 **28.** Change Lines 510 to 516 to read:

738 “ 4. *Control of Outsourced Operations and Suppliers of Materials’*  
739  
740

741 When outsourcing, a second party is hired under a contract to perform the operational processes  
742 that are part of a manufacturer’s inherent responsibilities. For example, a manufacturer may hire  
743 another firm to package and label or perform CGMP regulation training. Quality systems call for  
744 contracts (quality agreements) that clearly describe the materials or service, quality specifications  
745 responsibilities, and communication mechanisms. *In all cases, including purchased*  
746 *materials, the CGMP regulations hold the quality unit of the pharmaceutical*  
747 *manufacturer responsible for ensuring the adherence to quality by the second party be*  
748 *it material vendor or contract operator.”*  
749

750 This commenter knows that suppliers of materials also fall under the  
751 same controls as those appropriate for outsourced operations.

752 To address this reality, this commenter has added text that addresses  
753 materials’ suppliers because this is often not the case with some  
754 manufacturers especially when it comes to the area of setting contract  
755 specifications for a given purchased component.  
756

757 **29.** Change Lines 518 to 524 to read:

758 “Under a quality system, the *product* manufacturer ensures that the *contracted* firm is qualified.  
759 The *contracted* firm’s personnel should be adequately trained and monitored for performance  
760 according to their quality system, and the *contracted* firm’s and contracting manufacturer’s  
761 quality standards should not conflict. It is critical in a quality system to ensure that the  
762 contracting manufacturer’s officers are familiar with the specifics requirements of the contract.  
763 However, under the CGMP requirements, the QCU is responsible for approving or rejecting  
764 products or services provided under contract (see § 211.22(a)).”  
765  
766

---

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

767 The minor changes proposed in the text are offered to improve the  
 768 grammar, readability, and accuracy of the draft’s text.  
 769

770 **30.** Change Table following Line 529 to read:  
 771

21 CFR CGMP Regulations Related to Resources	
Quality System Element	Regulatory Citation
1. General Arrangements	—
2. Develop Personnel	Qualifications: § 211.25(a)
	Staff number: § 211.25(c)
	Staff training: § 211.25(a-b)
3. Facilities and Equipment	Buildings and facilities: § 211.22(b), 211.28(c), 211.42-211.58, and 211.173
	Equipment: § 211.63 – 211.72, 211.105, 211.160(b)(4), and 211.182
	Lab facilities: § 211.22(b)
4. Control of Outsourced Operations & Incoming Materials	Consultants: § 211.34
	Outsourcing: § 211.22(a)
	Incoming materials § 211.84(d)(2) & (3)

772 Changes in this Table were made to improve grammar and align Table  
 773 with changes in the text that added Incoming Materials to the Table’s **Point**  
 774 **4.**  
 775  
 776

777 **31.** Change Lines 547 to 549 to read:

778 “211.100). It is important to establish *the* responsibility for designing or changing products  
 779 *with personnel who understand the manufacturer’s quality systems and the requirement*  
 780 *minimums of the applicable CGMP regulations. If quality is to be truly built into a*  
 781 *product, the “building in” process must start at the beginning of the product design*  
 782 *phase. This is the case because adding quality later is more difficult and costly, and*  
 783 *may not be possible to accomplish. Documenting associated processes ~~will~~ should ensure*  
 784 *that all critical variables are identified and, to the extent required, properly controlled. This*  
 785 *documentation should include:*”  
 786  
 787

788 The changes proposed reflect this commenter’s decades of experience  
 789 in all phases of the design, development, implementation and control of a  
 790 process in a manner that ensures the released products meet their quality  
 791 expectations.  
 792

793 **32.** Change Lines 560 to 565 to read:

794 “As discussed under section IV.A. Management, above, the model calls for managers to ensure  
 795 that product specifications and process parameters are *scientifically sound and appropriate as*  
 796 *determined by the appropriate technical experts (e.g., engineers, development scientists). In the*  
 797 *pharmaceutical environment, experts ~~will~~ should have an understanding of the CGMP*  
 798 *minimums, pharmaceutical science, risk factors, and manufacturing processes as well as how*  
 799 *variations in materials and processes can ultimately affect the finished product and/or the*  
 800 *attainment of the CGMP minimums. One key CGMP minimum that must be*  
 801 *appropriately addressed in development is the requirement that each batch must be*  
 802

803 formulated with the intent to provide not less than 100 percent of the labeled or  
804 established amount of active ingredient (see § 211.101(a)).  
805

806 The changes suggested are offered because they clearly reflect the need  
807 for the quality system approach used to be fully CGMP-compliant.  
808

809 **33.** Restructure Lines 567 to 771 as follows:

810 “ 2. Examine Inputs

811 In modern quality systems models, the term *input* refers to any material that goes into a final  
812 product, no matter whether the material is purchased by the manufacturer or produced by the  
813 manufacturer for the purpose of processing. *Materials* can include items such as components  
814 (e.g., ingredients, process water, and gas), containers, and closures. A robust quality system will  
815 ensure that all inputs to the manufacturing process are reliable because quality controls will have  
816 been established for the receipt, production, storage, and use of all inputs.”  
817

818 This commenter recommends placing the examination of inputs after  
819 the “Design and Development” point instead of later to: **a)** match the  
820 structure in the applicable CGMP regulations and **b)** recognize that labels  
821 and labeling materials are *inputs*.  
822

823 “The quality systems model calls for the verification of the components and services provided by  
824 suppliers and contractors; however, the model offers a method for implementing verification that  
825 is different from those in the CGMP regulations.  
826

827 The CGMP regulations require either testing or use of a ~~certificate~~ report of analysis (ROA),  
828 commonly called a certificate of analysis (COA) by the industry, ~~plus an identity analysis~~  
829 provided that at least one specific identity test is conducted on such component by the  
830 manufacturer, and provided that the manufacturer establishes the reliability of the  
831 supplier's analyses through appropriate validation of the supplier's test results at  
832 appropriate intervals (see §§ 211.22 and 211.84). In the preamble to the CGMP regulations  
833 (see comment 239 in the preamble), these requirements were explicitly interpreted. The  
834 preamble states that reliability can be validated by conducting tests or examinations and  
835 comparing the results to the supplier's ROA. Sufficient initial tests must be done to establish  
836 reliability and to determine a schedule for periodic rechecking.”  
837

838 This commenter suggests correcting the Draft's text to reflect what the  
839 CGMP regulations actually require.  
840

841 “However, if the ROA option is pursued, at least one **specific** identity test is required to  
842 be conducted on representative samples of each shipment of each lot (see 21 CFR Sec.  
843 211.84(d)(2) and 21 CFR Sec. 211.160(b)(1)). [**Note:** The USP's IDENTIFICATION tests  
844 are, in general, **not** identity tests much less specific identity tests and, unless proven to be  
845 specific identity tests, cannot be used to comply with 21 CFR Sec. 211.84(d)(2).] In addition,  
846 to be used for acceptance in lieu of evaluation, the supplier's ROA must reflect  
847 adequate controls for each process critical variable factor (including, for the active  
848 pharmaceutical ingredients, the “as is” weight-percent purity) in the manufacturing  
849 process or processes in which it is intended to be used and certify that each lot was  
850  
851

852 made in accordance with the applicable CGMP since, by definition, drug components  
853 are drugs (see 21 U.S.C. Sec. 321(g)(1)(D)). As an essential element of purchasing  
854 controls, it is recommended that data for acceptance and rejection of materials be analyzed for  
855 information on supplier performance.<sup>13</sup> In addition, the manufacturer's quality unit is  
856 responsible for approving the tests and specifications for all materials (see 21 CFR Sec.  
857 211.22(a)).”

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

863 Specifically, the CGMP requirement *minimum* that each of the  
864 *representative samples* sampled from each shipment of each lot **must** be  
865 evaluated using a *specific identity test* (and not the USP's IDENTIFICATION  
866 tests [that are **not** *specific identity tests* and, *in most cases*, are **not** even  
867 *identity tests*]) and the CGMP requirement *minimum* that, where  
868 appropriate, the ROA **must** report the “as is” weight-percent purity of the  
869 component are clearly delineated.

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

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

887 “Under a quality systems approach, there should be procedures to verify that materials are from  
888 approved sources (for application and licensed products, certain sources are specified in the  
889 submissions). Procedures should also be established to encompass the acceptance, use, or the  
890 rejection and disposition of materials produced by the facility (e.g., purified water). Systems that  
891 produce these in-house materials should be designed, maintained, qualified, and validated ~~where~~  
892 ~~appropriate~~ to ensure the materials meet their acceptance criteria.”

894 Since this commenter knows of no instance where systems that produce  
895 in-house materials do **not** have to be proven to have produced an

---

<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.

896 acceptable material before that material can be used, this commenter has  
897 stricken the phrase “where appropriate.”  
898

899 “In addition, we recommend that changes to materials (e.g., specification, supplier, or materials  
900 handling) be implemented through a change control system (certain changes require review and  
901 approval by the quality control unit (see § 211.100(a)). It is also important to have a system in  
902 place to respond to changes in materials from suppliers so that necessary adjustments to the  
903 process can be made and unintended consequences prevented.”  
904

905 3. *Perform and Monitor Operations*  
906

907 The core purpose of implementing a *CGMP-compliant* quality systems approach is to enable a  
908 manufacturer to more efficiently and effectively perform, ~~and~~ monitor *and validate* operations  
909 (21 CFR Sec. 211.110(a)). The goal of establishing, adhering to, measuring, and  
910 documenting specifications and process parameters is to objectively assess whether an operation  
911 is meeting its design (and product performance) objectives. In a robust quality system,  
912 production and *in-process* controls should be designed to ensure that the finished products have  
913 the identity, strength, quality and purity they purport or are represented to possess (CGMP also  
914 requires this; see § 211.100(a)).”  
915

916 These changes were made to ensure that the context is that of a CGMP-  
917 compliant quality system.  
918

919 “In a modern quality system, a design concept established during product development typically  
920 matures into a commercial design after process experimentation and progressive modification.  
921 Areas of process weakness should be identified, and factors that are influential on critical quality  
922 attributes should receive increased scrutiny. (The FDA recommends that scale-up studies be  
923 used to help demonstrate that a fundamentally sound *design* has been fully realized.) A  
924 sufficiently robust manufacturing process should be in place prior to commercial production.  
925 With proper design (see section IV.C.1), and reliable mechanisms to transfer process knowledge  
926 from development to commercial production, a manufacturer should be able to validate the  
927 manufacturing process.<sup>14</sup> In a quality system, process validation provides initial proof, through  
928 commercial batch manufacture, that the design of the process produces the intended product  
929 quality. Sufficient testing data will provide essential information on performance of the new  
930 process, as well as a mechanism for continuous improvement. Modern equipment with the  
931 potential for continuous monitoring and control can further enhance this knowledge base.  
932 Although initial commercial batches can provide evidence to support the validity and consistency  
933 of the process,<sup>15</sup> the *entire life cycle* should be addressed by the establishment of continuous  
934 improvement mechanisms in the quality system.<sup>16</sup> Thus, in accordance with the quality systems  
935 approach, process validation is not a one time event, but an activity that continues.”  
936

937 The phrase “life cycle” should only be hyphenated (“life-cycle”) when it  
938 is used as an adjective phrase (e.g., life-cycle journey).  
939

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

<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 #8.

940 “As experience is gained in commercial production, opportunities for process improvements may  
941 become evident. (CGMP regulations at § 211.180 require the review and evaluation of records  
942 to determine the need for any change. These records contain data and information from  
943 production that provide insights into the product’s state of control. Change control systems  
944 should provide for a dependable mechanism for prompt implementation of technically sound  
945 manufacturing improvements.)  
946

947 Under a quality system, written procedures are followed and deviations from them are justified  
948 and documented (CGMP requires this; see § 211.100(b)) to ensure that the manufacturer can  
949 trace the history of the product, as appropriate, concerning personnel, materials, equipment, and  
950 chronology and that processes for product release are complete and recorded.  
951

952 Both the CGMP regulations (see § 211.110) and quality systems models call for the monitoring  
953 of critical process parameters during production.  
954

- 955 • Process steps should be verified using a validated computer system or a second person.  
956 Batch production records should be prepared contemporaneously with each phase of  
957 production. Although time limits can be established when they are important to the  
958 quality of the finished product (CGMP addresses this; see § 211.111), this does not  
959 preclude the ability to establish production controls based on in-process parameters that  
960 can be based on desired process endpoints measured using real time testing or monitoring  
961 apparatus (e.g., blend until mixed vs. blend for 10 minutes).
- 962 • Procedures should be in place to prevent objectionable microorganisms in finished  
963 product that is not required to be sterile and to prevent microbial contamination of  
964 finished products purported to be sterile (CGMP also requires this; see § 211.113)  
965 Sterilization processes should be validated (CGMP also requires this; see § 211.113(b))  
966 for sterile drugs.<sup>17</sup>

967 Though part of the manufacturing process, the CGMP regulations for finished  
968 pharmaceuticals explicitly separate the final evaluation of the each batch for its  
969 acceptability for release for distribution from the other aspects of the quality  
970 system. Under CGMP, an explicit set of requirements must be met before a  
971 batch can be released (see §§ 211.165 and 211.167). Since the CGMP  
972 regulations specifically require the use of *statistical quality control criteria* that  
973 include *appropriate acceptance levels* and/or *appropriate rejection levels*, the  
974 *minimum* level of quality is that established by the *appropriate* use of *statistical*  
975 *quality control* (§ 211.165(d)) on the results obtained for each critical product  
976 quality factor on a *batch-representative* set of samples (§ 211.160(b)(3)). Thus,  
977 under CGMP, *batch-representative statistical quality control* based on all of the  
978 critical quality characteristics of the *representative samples* evaluated is the  
979 minimum level of quality that is acceptable for deciding whether or not a batch is  
980 *acceptable for release for distribution*. Therefore, all CGMP-compliant quality  
981 systems must meet, or exceed, the *statistical quality control criteria* for each critical  
982 variable factor derived from the evaluation of an appropriately *batch-representative*  
983 *sample* set for that variable factor where the number of samples tested for each  
984 variable factor depends upon the size of the batch, the minimum established

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<sup>17</sup> See Reference # 8.

985 acceptance quality level, the level of process reproducibility established by the  
986 product's history, and the confidence level (95 % or above) that the manufacturer  
987 elects to use to ensure that each batch has a high degree of assurance that each  
988 unit in that batch, if tested, will meet its lifetime specifications at any point  
989 including at its expiration date.

991 This section was added to ensure that all parties clearly understand  
992 what the CGMP minimums are with regard to batch acceptance for release.

993  
994 “Pharmaceutical products must meet their specifications and manufacturing processes must  
995 consistently meet their parameters. Under a quality system, selected data are used to evaluate the  
996 quality of a process or product. In addition, data collection can provide a means to encourage  
997 and analyze potential suggestions for improvement. A quality systems approach calls for the  
998 manufacturer to develop procedures that monitor, measure, and analyze the operations (including  
999 analytical methods and/or statistical techniques). Knowledge continues to accumulate from  
1000 development through the entire commercial life of the product. Significant unanticipated  
1001 variables should be detected by a well-managed quality system and adjustments implemented.  
1002 Procedures should be revisited as needed to refine operational design based on new knowledge.  
1003 Process understanding increases with experience and helps identify the need for change towards  
1004 continuous improvement *in the quality of the drug product produced*. When implementing  
1005 data collection procedures, consider the following:  
1006

- 1007 • Are collection methods documented?
- 1008 • When in the product's life cycle will the data be collected?
- 1009 • How and to whom will measurement and monitoring activities be assigned?
- 1010 • When should analysis and evaluation (e.g. trending) of laboratory data be performed  
1011 (see V.E.1.)?
- 1012 • What records are needed?”

1013 The first change suggested clarifies what the overriding goal of a CGMP-  
1014 compliant quality system should be.

1015 The second change, in the second bullet, simply corrects the grammar.

1016  
1017 “A modern quality system approach indicates that change control is warranted when data  
1018 analysis or other information reveals an area needing improvement. Changes to an established  
1019 process should be controlled and documented to ensure that desired attributes for the finished  
1020 product will be met (CGMP also requires this; see § 211.100(a)).  
1021

1022 Change control with regard to pharmaceuticals is addressed in more detail in the CGMP  
1023 *regulations*. When developing a process change, it is important to keep the process design and  
1024 scientific knowledge of the product in mind. When major design issues are encountered through  
1025 process experience, a firm may need to revisit the adequacy of the design of the manufacturing  
1026 facility (§ 211.42), the design of the manufacturing equipment (§ 211.63), the design of the  
1027 production and control procedures (§ 211.100), or the design of laboratory controls (§ 211.160).  
1028 When implementing a change, determining its effect should be based on monitoring and  
1029 evaluating those specific elements that may be affected based on understanding of the process.  
1030 This allows the steps taken to implement a change and the effects of the change on the process to

1031 be considered systematically. Evaluating the effects of a change can entail additional tests or  
1032 examinations of subsequent batches (e.g., additional in-process testing or additional stability  
1033 studies).  
1034

1035 The quality system elements identified in this guidance, if implemented, will help a manufacturer  
1036 manage change and implement continuous improvement in manufacturing.  
1037

1038 Under a quality system, procedures should be in place to ensure the accuracy of test results. Test  
1039 results that are out of specification may be due to testing problems or manufacturing problems  
1040 and should be investigated.<sup>18</sup> Invalidation of test results should be: a) scientifically ~~and~~  
1041 ~~statistically~~ sound, b) based on an analyst error, method weakness, or equipment failure  
1042 established from the critical evaluation (investigation) of all data, and c) justified. [**Note:**  
1043 To facilitate the critical evaluation of data, the manufacturer’s laboratory operations (in-house  
1044 and contract) should establish a system that identifiably links the specific equipment,  
1045 materials, personnel, method execution steps, and other factors that may affect outcomes to  
1046 each result value generated.]”  
1047

1048 The changes suggested reflect the reality that, in a robust CGMP-  
1049 compliant quality system, conclusive proof of a cause must be found before  
1050 test results can be “invalidated.”

1051 This is the case because robust quality systems provide the requisite  
1052 controls that ensure that the validity of any test result can be proven to be  
1053 valid or invalid.

1054 The draft’s existing text did **not** make the preceding reality crystal clear  
1055 and its unfortunate use of the phrase, “scientifically and statistically sound,”  
1056 attempts to establish an untenable non-existent dichotomy between  
1057 science and statistics.

1058 Factually, since the term scientifically sound encompasses all proper  
1059 uses of statistics, the phrase, “scientifically and statistically sound,” is an  
1060 illogical and grammatically incorrect construction.  
1061

1062 “The Agency recommends that, upon the completion of manufacturing and to maintain quality,  
1063 the manufacturer should consider shipment requirements to meet special handling needs (in the  
1064 case of pharmaceuticals, one example might be refrigeration).  
1065

1066 Under a quality system, trends should be continually identified and evaluated. One way of  
1067 accomplishing this is the use of statistical process control. The information from trend analyses  
1068 can be used to continually monitor quality, identify potential variances before they become  
1069 problems, bolster data already collected for the annual review, and facilitate improvement  
1070 throughout the product life cycle. *On-going minimum process capability* assessment can serve  
1071 as a basis for determining the need for changes that can result in process improvements and  
1072 efficiency (see IV.D.1.).”  
1073

1074 The term “life cycle” should **not** be hyphenated here.

1075 The commenter’s addition of the phrase “*on-going minimum*” is  
1076 designed to convey two realities:

---

<sup>18</sup> See Reference #9

- 1077 1. Under a quality system’s approach, all process assessments are *on-*  
1078 *going* activities, and  
1079 2. To be *scientifically sound* and *CGMP-compliant*, the *process capability*  
1080 approach used must address the *minimum capability* of the process.  
1081

1082 “ 4. *Monitor Packaging and Labeling Processes*  
1083

1084 Packaging and labeling controls, critical stages in the pharmaceutical manufacturing process, are  
1085 not specifically addressed in quality systems models. Therefore, the Agency recommends that  
1086 manufacturers always refer to the packaging and labeling control regulations at 21 CFR 211  
1087 Subpart G. In addition — and this *is* consistent with modern quality systems — FDA  
1088 recommends that, as part of the design process, before commercial production, the controls for  
1089 all processes within the packaging and labeling system be planned and documented in written  
1090 procedures. The procedures should outline quality control activities and the responsible  
1091 positions. Specifications and controls for the packaging and labeling materials should also be  
1092 determined before commercial production. Distinct labels with discriminating features for  
1093 different products, such as a product marketed with different strengths, should be included to  
1094 prevent mislabeling and resulting recalls.”  
1095

1096 The commenter changed the section number to reflect its suggested  
1097 placement.  
1098

1099 “ 5. *Expiration Dating and Stability Assessment*  
1100

1101 Unlike most quality systems, the CGMP regulations explicitly address the  
1102 intertwined quality issues of expiration dating and stability evaluation. To  
1103 establish a viable expiration date (see § 211.137), the stability of the drug  
1104 product must be evaluated (see § 211.166). Moreover, the ongoing assessment  
1105 of stability should, at a minimum, be an adjunct to the ‘annual review’ process  
1106 (see § 180(e)). Moreover, the stability evaluation must test a statistically valid  
1107 number of batch representative samples (§ 211.160(b)(3)) must be tested for  
1108 each critical quality characteristic at suitable intervals (see § 211.166(a)(1)).”  
1109

1110 This section was added to address relevant quality system issues for  
1111 CGMP-compliant manufacturers that, for some non-obvious reason, the  
1112 draft failed to address.  
1113

1114 “ 6. *Address Nonconformities*  
1115

1116 A key component in any quality system is handling nonconformities and/or deviations. The  
1117 investigation, conclusion, and follow-up should be documented (CGMP also requires this; see 21  
1118 CFR 211.192). To ensure that a product conforms to requirements and expectations, it is  
1119 important to measure process and the product attributes (e.g., specified control parameters  
1120 strength) as planned. Discrepancies may be detected during any stage of the process by an  
1121 employee or during quality control activities. Not all discrepancies will result in product defects;  
1122 however, it is important to document and handle them appropriately. A discrepancy investigation  
1123 process is critical when a discrepancy is found that affects product quality (CGMP also requires  
1124 this; see § 211.192).  
1125

1126 In a quality system, it is critical to develop and document procedures to define responsibilities  
 1127 for halting and resuming operations, recording the nonconformity, investigating the discrepancy,  
 1128 and taking remedial action. The corrected product or process should also be re-examined for  
 1129 conformance and assessed for the significance of the nonconformity (CGMP also requires this;  
 1130 see § 211.115). If the nonconformity is significant, based on consequences to process efficiency,  
 1131 product quality, safety, and availability, it is important to evaluate how to prevent recurrence.  
 1132

1133 Under a quality system, if a product or process does not meet requirements and has not been  
 1134 released for use, it is essential to identify or segregate it so that it is not distributed to the  
 1135 customer by accident. Remedial action may include correcting the nonconformity; or, with  
 1136 proper authorization, allowing the product to proceed with proper authorization and the problem  
 1137 documented, or using the product for another application; or rejecting the product. If an  
 1138 individual product that does not meet requirements has been released, the product can be  
 1139 recalled.<sup>9</sup> Customer complaints should be handled as discrepancies and be investigated (CGMP  
 1140 addresses this; see § 211.198).”  
 1141

1142 The commenter changed the section number to reflect its suggested  
 1143 placement.  
 1144

1145 “ 7. *Process Improvement*  
 1146

1147 In modern quality systems environments, when new or reengineered processes ~~es~~ steps are  
 1148 developed, it is expected that they will be designed in a controlled manner. A design plan would  
 1149 include authorities and responsibilities; design and development stages; and appropriate review,  
 1150 verification, and validation. If different groups are involved in design and development, the  
 1151 model recommends that responsibilities of the different groups be documented to avoid omission  
 1152 of key duties and ensure that the groups communicate effectively. Plans should be updated when  
 1153 needed during the design process. Prior to implementation of processes (or shipment of a  
 1154 product), a robust quality system will ensure that the process and product will perform as  
 1155 intended. Change controls should be maintained throughout the design *and design*  
 1156 *implementation process.*”  
 1157

1158 The commenter changed the section number to reflect its suggested  
 1159 placement.

1160 The commenter also revised the text slightly to: **a)** explicitly place the  
 1161 requirement for control at the process step level and **b)** ensure that “change  
 1162 controls” are maintained throughout the design implementation process.  
 1163

1164 **34.** Change Table following Line 776 to read:  
 1165

21 CFR CGMP Regulations Related to Manufacturing Operations	
Quality System Element	Regulatory Citation
1. Design and Develop Product and Processes	Production: § 211.100(a)
2. Examine Inputs	Materials: §§ 210.3(b), 211.80 – 211.94, 211.101, 211.122, and 211.125
3. Perform and Monitor Operations	Production: §§ 211.100, 211.103, 211.110, 211.111, and 211.113

<sup>9</sup> See 21 CFR Part 7

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	QC criteria: §§ 211.22(a-c), 211.115(b), 211.160(a), 211.160(b), 211.165(a)-(c), and 211.165(d)
	QC checkpoints: §§ 211.22 (a), 211.84(a), 211.87, 211.110(c), 211.165, and, for some products, 211.167.
4. Monitor Packaging and Labeling Processes	CGMP requirements: § Subpart G
5. Expiration Dating and Stability Assessment	CGMP requirements: §§ 211.137 and 211.166
6. Address Nonconformities	Discrepancy investigation: §§ 211.22(a), 211.115, 211.192, and 211.198 Recalls: 21 CFR Part 7
7. Process Improvement	QC involvement: §§ 211.22(a), 211.115(b), and 211.160(a)

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1167  
1168  
1169  
1170  
1171

Changes in this Table were made to improve grammar and align Table with changes in the text.

In addition, the extra line in this Table’s heading was removed to align its format to match the format of the previous two (2) similar Tables.

1172

**35.** Change Lines 794 to 799 to read:

1173  
1174  
1175  
1176  
1177  
1178  
1179  
1180  
1181  
1182

“Although the *minimum periodic* ~~annual~~ review required in the CGMP regulations (§ 211.180(e)) calls for review of representative batches *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. Trending enables the detection of potential problems as early as possible to plan corrective and preventive actions. Another important concept of modern quality systems is the use of trending to examine processes as a whole; this is consistent with the annual review approach. These trending analyses can help focus internal audits (see IV.D.2).”

1183  
1184  
1185  
1186

This commenter notes that draft fails to accurately reflect the CGMP requirement *minimum* in this case and has changed the text to reflect what the CGMP regulations actually require to be included in an annual review.

1187

**36.** Change Lines 801 to 507 to read:

1188  
1189  
1190

“ 2. Conduct Internal Audits

1191  
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1203

A quality systems approach calls for audits to be conducted at planned intervals to evaluate effective implementation and maintenance of the quality system and to determine if processes and products meet established parameters and specifications. As with other procedures, audit procedures should be developed and documented to ensure that the planned audit schedule takes into account the relative risks of the various quality system activities, the results of previous audits and corrective actions, and the need to audit the entire system at least annually. Quality systems recommend that procedures describe how auditors are trained in objective evidence gathering, their responsibilities, and auditing procedures. Procedures should also define auditing activities such as the scope and methodology of the audit, selection of auditors, and audit conduct (audit plans, opening meetings, interviews, closing meeting and reports). It is critical to maintain records of audit findings and assign responsibility for follow-up to prevent problems from recurring (see IV.D.3.).

1204 The quality systems model calls for managers who are responsible for the areas audited to take  
 1205 timely action to resolve audit findings and ensure that follow-up actions are completed, verified,  
 1206 and recorded. (FDA’s policy is to not routinely review or copy reports and records that result  
 1207 from internal audits per Compliance Policy Guide 130.300.<sup>20</sup>)  
 1208

1209 The section’s heading was changed from “... Audit” to “... Audits” to  
 1210 match the subject discussed, *audits*.  
 1211

1212 **37.** Change Table following Line 881 to read:  
 1213

21 CFR CGMP Regulations Related to Evaluation Activities	
Quality System Element	Regulatory Citation
1. Analyze Data for Trends	Annual Review: § 211.180(e)
2. Conduct Internal Audits	Annual Review: § 211.180(e)
3. Risk Assessment	Sampling and testing of in-process materials and drug products § 211.110(b) Testing and Release for Distribution § 211.165(d)
4. Corrective Action	Discrepancy investigation: § 211.22(a), 211.192
5. Preventive Action	—
6. Promote Improvement	—

1214 Additions to this Table were made to reflect those sections of the CGMP  
 1215 regulations that are, in some form, risk assessments.  
 1216  
 1217

1218 **38.** Change Lines 893 to 899 to read:  
 1219

1220 “characteristics, each of which have been discussed in detail above:  
 1221

- 1222 • ~~Science-based~~ *Scientifically sound and appropriate* approaches
- 1223 • Decisions based on an understanding of the intended use of a product
- 1224 • Proper identification and control of areas of potential process weakness
- 1225 • Responsive deviation and investigation systems that lead to timely remediation
- 1226 • Sound methods for assessing *and reducing* risk”

1227 In the first bullet, this commenter replaced the undefined and off-  
 1228 misused phrase, “science-based” with the CGMP quality approach that  
 1229 requires all such to be *scientifically sound and appropriate*.

1230 In the second instance, this commenter added the phrase “and  
 1231 reducing” to reflect the reality that, with respect to risk, there also need to  
 1232 be methods for reducing the risk.  
 1233

1234 **39.** Change Lines 946 to 947 to read:  
 1235

1236 “14. ~~ANSI~~ISO/IEC 17025:1999: General requirements for the competence of testing and  
 1237 calibration laboratories (*adopted by American Society for Quality as the American  
 1238 Standard in 1999*)  
 1239

1240 This commenter could find no listing on the ASQ site that listed the  
 1241 standard as other than “ISO/IEC 17025:1999.”

<sup>20</sup> See Reference #10.

1242

1243 **40.** Change Lines 1016 to 1017 to read:

1245 “ **Correction** - Repair, rework, or adjustment ~~and relating~~ing to the disposition of an existing  
1246 discrepancy”

1247 This change in the draft was made to improve the accuracy of the  
1248 definition provided.

1249

1250 **41.** Change Lines 1022 to 1023 to read:

1251 “ **Customer** – a person or organization (internal or external) that receives a product or service  
1252 anywhere along the product’s life cycle.”

1253 This commenter removed the hyphen “-“ between life and cycle to  
1254 make the definition grammatically correct.

1255 The hyphen is only appropriate when the term “life cycle” is used as an  
1256 adjective (e.g., life-cycle approach).

1257

1258 **42.** After Line 1031, insert the following:

1259 “ **Minimum Process Capability** – in general, the established specification range  
1260 for a given quality characteristic divided by six times the uncertainty adjusted  
1261 estimate of the standard deviation computed. In cases, like drug products,  
1262 where the target value is not centered in the established specification range, a  
1263 “*minimum process capability index*” approach should be used. In general, the  
1264 *minimum process capability index* is defined as a half-range divided by three  
1265 times the uncertainty-adjusted estimate of the standard deviation computed. In  
1266 almost all cases, the half range is the predetermined upper specification limit  
1267 minus the target value for the characteristic being evaluated.

1268 This term was added to the glossary to define a term that this  
1269 commenter introduced in one of his proposed changes.

1270

1271 **43.** Change Lines 1053 to 1054 to read:

1272 “ **Quality Control** – ~~the steps taken during the generation of a product or service to ensure that it~~  
1273 ~~meets requirements and that the product or service is reproducible~~ a system of verifying and  
1274 maintaining a desired level of quality in a product or process by careful planning, use  
1275 of proper equipment, continued inspection, and corrective action as required.

1276 This commenter changed the definition to match the dictionary  
1277 definition of *quality control* because that definition fits the CGMP view of the  
1278 term much better than the definition provided in the draft.

1279

1280 **44.** After Line 1088, insert the following:

1281 “ **Statistical Quality Control** – A tool of industrial management, comparable with  
1282 *production control* and *cost control*, which uses the evaluation of *population*  
1283 *representative evaluations* and *population statistics* to ensure manufacturing of a  
1284 product produces a product that consistently meets its acceptance  
1285 specifications for the finished product.

1286

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1295            This term was added to the glossary to define a term that: **a)** this draft  
1296            used but id not define and **b)** carries with it requirements that most in the  
1297            pharmaceutical industry seeming to knowingly, or otherwise, ignore.  
1298