

Facility Automation Information Management (FAME) Systems

Tuesday, 18 January 2005

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

RE: Docket No. 2004D-0443

FORMAL COMMENT TO:

Docket Number: 2004D-0443

Comment To : "Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations"

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

BACKGROUND

On 15 November 2003, **FAME Systems** provided comments to this docket based on an in-depth reading of the FDA's "**Draft Guidance for Industry on Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations** [G:\6452dft.doc 9/28/04]."

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current good manufacturing practice (CGMP), in general, and the drug CGMP and other regulations with which the Agency's draft guidance is required to be congruent.

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

- ❖ Has reviewed the formal comments, *other than those submitted by **FAME Systems***, available electronically in Public Docket 2004D-0443 as of Saturday, 15 January 2005.
- ❖ Has prepared and submitted **FAME Systems'** scientific and CGMP-conformance assessment of those formal comments.
- ❖ Has prepared and is now submitting **FAME Systems'** revised draft of the published draft guidance that incorporates all of the constructive comments that were submitted to: **a)** aid to the Agency in revising the originally published draft guidance **and b)** shorten the review period for this guidance.

To clearly separate **FAME Systems'** changes from the original draft guidance issued by the FDA, the proposed changes are in a **red Century** font and, in those instances where a deletion has been made, the original Times New Roman font for the words on either side of the deletion are changed to a **red Times New Roman** font.

Facility Automation Information Management (FAME) Systems

Should anyone who reads this *revised draft* of “**Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations**,” find that its suggested alternatives are at odds with sound inspection science or the applicable CGMP regulations, or that additional clarification is needed in a given area, then, *in addition to providing the sound science or rationale that refutes the revised text or his or her clarifying comments to the public docket*, he or she is asked to e-mail **drking@dr-king.com** a copy of that sound science, rationale, and/or commentary.

Respectfully submitted,

Dr. King

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Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

REVISED DRAFT GUIDANCE

This **revised** draft guidance document is being **submitted** for **FDA review** purposes.

~~Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.~~

For questions regarding this draft document contact ~~(CDER) Monica Caphart, 301-827-9047; (CBER) Robert Sausville, 301-827-6201; (CVM) June Liang, 301-827-8789; and (ORA) Patricia Maroney-Benassi, 240-632-6819.~~ **(FAME Systems) Dr. King, 973-263-4843**

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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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January 2005
Pharmaceutical CGMP Regulations

Guidance for Industry

Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

~~Additional copies are available from:
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34 **A. Background**

35 In August 2002, the FDA announced the “Pharmaceutical CGMPs for the 21st Century
36 Initiative.” In that announcement, the FDA explained the Agency’s intent to integrate *quality*
37 *systems* and *risk management* approaches into existing programs with the goal of encouraging
38 the adoption of **state-of-the-practice** and innovative manufacturing technologies. The CGMP
39 initiative was spurred by the fact that since 1978, when the last major revision of the CGMP
40 regulations was published, there have **been advances** in manufacturing technologies and in our
41 understanding of quality systems. Many pharmaceutical manufacturers are implementing
42 **comprehensive quality** systems and risk management approaches. The Agency also saw a need
43 to address the harmonization of the **CGMP regulations** and other non-U.S. pharmaceutical
44 regulatory systems as well as FDA’s own medical device quality systems regulations.

45 The CGMP initiative steering committee created a Quality System Guidance Development
46 working group (QS working group) to compare the current CGMP regulations, which call for
47 specific quality management elements, to other existing quality management systems. The QS
48 working group mapped the relationship between CGMP regulations (**Parts** 210 and 211 and the
49 1978 Preamble to the CGMP regulations²) and various quality system models, such as the Drug
50 Manufacturing Inspections Program (i.e., systems-based inspectional program),³ the
51 Environmental Protection Agency’s Guidance for Developing Quality Systems for
52 Environmental Programs, ISO Quality Standards, other quality publications, and experience
53 from regulatory cases. The QS working group determined that, although the regulations do
54 provide great flexibility, the CGMP regulations do not consider all of the elements that today
55 constitute most quality management systems. The CGMP regulations and other systems differ
56 somewhat in organization and in certain constituent elements; however, they are very similar and
57 share underlying **principles**. The QS working group decided that it would be very useful to
58 examine exactly how the CGMP regulations and the elements of a **comprehensive quality** system
59 fit together in today’s manufacturing world. This guidance is the result of that examination.

60 **B. Goal of the Guidance**

61 This guidance describes a comprehensive quality systems model, which, if **properly**
62 implemented, will allow manufacturers to operate **broad, robust quality** systems that are fully
63 compliant with CGMP regulations. The guidance demonstrates how and where the requirements
64 of the CGMP regulations fit within this comprehensive model. The inherent flexibility of the
65 CGMP regulations should enable manufacturers to implement a quality system in a form that is
66 appropriate for their specific operations.

67 The overarching philosophy articulated in both the CGMP regulations *and* in **robust quality**
68 systems is:

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

² See Reference #1.

³ See Reference #2.

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72 This guidance is intended to serve as a bridge between the 1978 regulations and our current
73 understanding of quality systems. In addition to being part of the FDA's CGMP initiative, this
74 guidance is being issued for a number of reasons:

- 75 • A quality system addresses the public and private sectors' mutual goal of providing a high-
76 quality drug product to patients and prescribers. A well-built quality system should prevent
77 or reduce the number of recalls, returned or salvaged products, and defective products
78 entering the marketplace.
- 79 • It is important that we harmonize the CGMP **regulations** to the extent possible with other
80 widely used quality management systems including **those addressed in the "ISO 9000"**
81 **set of standards**, non-U.S. pharmaceutical quality management requirements, and FDA's
82 own medical device quality system regulations. With the globalization of pharmaceutical
83 manufacturing and the increasing prevalence of drug- and biologic-device combination
84 products, the convergence of quality management principles across different regions and
85 among various product types is very desirable **provided the applicable CGMP**
86 **minimums are met**.
- 87 • The FDA has concluded that **today's** quality systems, when coupled with manufacturing
88 process and product knowledge, can handle many types of changes to facilities, equipment,
89 and processes without the need for a regulatory submission. Manufacturers with appropriate
90 process knowledge and a robust quality system should be able to implement many types of
91 improvements without the need for a prior regulatory filing. In addition, an effective quality
92 system, by lowering the risk of manufacturing problems, may result in shorter and fewer
93 FDA inspections.
- 94 • A **comprehensive** quality system can provide the necessary framework for implementing
95 *quality by design* (building in quality from the development phase and throughout a product's
96 life-cycle), continuous improvement, and risk management in the drug manufacturing
97 process. **The particular** quality system adopted by a manufacturer **should** be tailored to fit
98 the specific environment, taking into account factors such as scope of operations, complexity
99 of processes, and appropriate use of finite resources.

100 **C. Scope of the Guidance**

101 This guidance applies to **those engaged in any facet of the manufacture** of drug products
102 (finished pharmaceuticals), including products regulated by the Center for Biologics Evaluation
103 and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for
104 Veterinary Medicine (CVM). It may also be useful to manufacturers of **the** components used in
105 the manufacture of these products.

106 This document is **neither meant** to create new expectations for pharmaceutical manufacturing
107 that go beyond the requirements laid out in the current regulations **nor intended** to be a guide for
108 the conduct of FDA inspections. Rather, the document explains how implementing
109 comprehensive quality systems can help manufacturers achieve compliance with 21 CFR **Parts**
110 210 and 211. Although the QS working group found that many of the quality system elements
111 correlate with specific CGMP requirements, some do not. In the end, the Agency expects

112 compliance with the CGMP regulations. Thus, the FDA’s inspection program remains geared
113 to compliance with those regulations.

114 D. Organization of This Guidance

115 To provide a reference familiar to industry, the quality systems model described in this guidance
116 is organized — in its major sections — according to the structure of international quality
117 standards. Therefore, the major sections of the model used in this guidance are:

- 118 • Management Responsibilities
- 119 • Resources
- 120 • Manufacturing Operations
- 121 • Evaluation Activities

122 Within each of these sections, the key elements found in today’s quality systems are discussed.
123 When an element correlates with a CGMP regulatory requirement, we note that correlation. In
124 some cases, a specific CGMP regulation is discussed in more detail as it relates to a quality
125 system element. At the end of each section, a table is included listing the quality system
126 elements of that section and the specific CGMP regulations with which they correlate. A
127 glossary is included at the end of the document for those not familiar with the CGMP,
128 process, quality, and statistical terms defined therein.

129 III. CGMP AND THE CONCEPTS OF TODAY’S QUALITY SYSTEMS

130 CGMP is the acronym for “current good manufacturing practice,” as that phrase is used in
131 21 U.S.C. Section 351(a)(2)(B), the statutory foundation underlying the CGMP
132 regulations for drugs and finished pharmaceuticals that: a) establish the
133 requirement *minimums* for the manufacture, processing, packing or holding of drug
134 products and b) are the focus of the quality systems approach used in this guidance.

135 Similarly, several key concepts are critical for any discussion of today’s quality systems. The
136 following concepts, as they relate to the manufacture of pharmaceutical products, are the
137 important basis ideas used in this guidance.

138 A. Quality

139 Every pharmaceutical product has established identity, strength, purity, and other quality
140 characteristics designed to ensure the required levels of safety and effectiveness. For the
141 purposes of this guidance document, the phrase *achieving quality* means achieving these
142 characteristics for all the product units from the time these units are released until after
143 the units have passed their expiration date.

144 B. Quality by Design and Product Development

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

147 quality **criteria** at the end of the manufacturing process. A quality system provides a sound
148 framework for the transfer of process knowledge from development to the commercial
149 manufacturing processes and for post-development changes and optimization.

150 C. Risk Management and Risk Assessment

151 The concept *risk management* is a major focus of the “Pharmaceutical CGMPs for the 21st
152 Century Initiative.” Risk management can guide the setting of specifications and process
153 parameters. Risk assessment is also used in determining the need for discrepancy investigations
154 and corrective action. **When** risk assessment is used more formally by manufacturers, it **should**
155 be implemented within a quality system framework. **It should be noted that the CGMP**
156 **regulations for finished pharmaceuticals (21 CFR Part 211) establish risk-based**
157 **minimums** for components, processes, in-process materials, and drug-product
158 quality assessments for acceptability for release that, given their timeframe and
159 wording, set a minimum level of confidence that is **not less than 95%** – a level of
160 quality that is well below today’s recognized ‘de facto’ accepted performance
161 standard for quality excellence (‘Six Sigma’).

162 D. Systems Controls

163 Inherent in all quality management systems is the need to control the outcomes
164 observed by exerting various defined levels of direct and indirect control on the
165 inputs, processes, procedures, and processors that produce the desired outcomes. In
166 pharmaceutical manufacturing, “systems controls” is an overarching term used to
167 encompass all aspects of a quality system that innately control the degree to which
168 the process outcomes (in-process materials and products) *minimally* meet, or *ideally*
169 exceed, their expectations. When examined from the viewpoint of *systems controls*
170 or, simply, *controls*, it is obvious that the CGMP regulations for finished
171 pharmaceuticals (21 CFR Part 211) are control centric. **Figure 1** outlines the
172 *controls* organizational structure of the CGMP regulations for finished
173 pharmaceuticals. The umbrella regulations that encompass all of the basic controls
174 governing a firm’s finished pharmaceutical operations are contained in 21 CFR Sec.
175 211.160. Thus, when considered logically, it becomes clear that the fundamental
176 bases (foundation) for all of the manufacturer’s controls reside in 21 CFR Sec.
177 211.160, a section that is simply titled “**General requirements.**”

178 E. CAPA (Corrective **Action** and Preventive Action)

179 CAPA is a well-known CGMP regulatory concept that focuses on investigating and correcting
180 discrepancies and attempting to prevent **their** recurrence. Quality system models discuss CAPA
181 **in terms of** three concepts, all of which are used in this guidance. **Those three concepts are:**

- 182 • Remedial corrections
- 183 • Root cause analysis with corrective action to prevent recurrence
- 184 • Preventive action to prevent initial occurrence

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FIG. 1 - OVERVIEW OF THE CONTROLS STRUCTURE IN 21 CFR PART 211

[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)

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F. Change Control

222 *Change control* is another well-known CGMP regulatory concept that focuses on managing
223 change to prevent unintended consequences. Ideally, change control should be
224 incorporated into an ongoing journey-based approach to generating and
225 maintaining a process that continually operates in its validated (“proven valid”)
226 state. The major implementation of change control in the CGMP regulations is expressed in
227 the responsibilities assigned to the quality control unit. In addition, certain manufacturing
228 changes (e.g., changes that alter specifications or critical product characteristics, including
229 bioavailability) require regulatory filings and prior regulatory approval (§§ 601.12 and 314.70).

230 A quality system also contains change control activities, including quality planning and control
231 of revisions to specifications, process parameters, and procedures. In this guidance, *change* is
232 discussed in terms of creating a regulatory environment that encourages change and continuous
233 improvement in the process, without adversely affecting in-process integrity, or the
234 quality of the product. This means a manufacturer is empowered to make predetermined
235 changes in response to the permissible variability of materials used in manufacturing and
236 otherwise optimize the process based on the ongoing use of statistical control
237 techniques that permit the manufacture to separate the effect of critical
238 characteristic variation from random outcome fluctuation.

G. The Quality Unit

240 Many of the current quality systems ideas described in this section correlate very closely with
241 the CGMP regulations (refer to the charts later in the document). Current industry practice
242 generally divides the responsibilities of the Quality Control Unit (QCU), as defined in the CGMP
243 regulations, among the quality control (QC), quality assurance (QA) and regulatory affairs
244 (RA) functions.

- 245 • QC usually consists of assessing the suitability of incoming components,
246 containers, closures and labeling, critical in-process materials and the finished
247 products to evaluate the performance of the manufacturing process to ensure adherence to
248 proper specifications and limits, and to determine the acceptability of each lot or
249 batch for release.
- 250 • QA primarily includes the review and approval of all procedures related to production,
251 maintenance, and review of associated records, and auditing, and overseeing trend
252 analysis evaluations. In some firms, QA also determines the acceptability of
253 each batch or lot for release.
- 254 • RA typically acts as the quality function’s bi-directional interface between the
255 other quality functions and the FDA.

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256 This guidance uses the term *quality unit*⁴ (QU) to reflect **current** practice while remaining
257 consistent with the CGMP definition in 21 CFR **Sec.** 210.3(b)(15). The concept *quality unit* is
258 also consistent with **current** quality systems in ensuring that the various operations associated
259 with all systems are **scientifically sound, appropriate, and** appropriately **approved,**
260 **implemented,** conducted, **modified,** and monitored. The CGMP regulations specifically
261 assign the quality unit the authority to **review and approve** the quality system **and any**
262 **change thereto.** However, the quality unit is not meant to take on the responsibilities of other
263 units of a manufacturer's organization, such as the responsibilities handled by manufacturing
264 personnel, engineers, and development scientists.⁵

265 Under a robust quality system, the **product and process development units,** manufacturing
266 units, and the quality unit can remain independent, but **are all still included** in the total concept
267 of producing quality products. **Although staffing levels should be reflective of the size of**
268 **the operation, the number of individuals assigned to the quality control unit must**
269 **be sufficient to meet the requirements of 21 CFR § 211.22 and other applicable**
270 **regulations. The quality unit is accountable for reviewing, approving, and**
271 **overseeing the implementation of all the controls, and for ensuring that product**
272 **quality standards have been met.**

273 Other CGMP assigned responsibilities of the quality unit are consistent with **current** quality
274 system approaches (see § 211.22) **and include:**

- 275 • **Ensuring the controls are scientifically sound and appropriate as well as**
276 **ensuring that the samples sampled and the samples evaluated are**
277 **representative of the population (batch or lot) from which they are taken.**
- 278 • Ensuring that controls are implemented and completed satisfactorily during
279 manufacturing operations
- 280 • Ensuring that developed procedures and specifications are appropriate and followed,
281 including those used by a firm under contract to the manufacturer
- 282 • Approving or rejecting **incoming and** in-process materials, and drug products —
283 although such activities do not substitute for, or preclude, the daily responsibility of
284 manufacturing personnel to build quality into the product
- 285 • Reviewing production records and **overseeing the investigation of** any unexplained
286 discrepancies
- 287 • **Ensuring a CGMP-compliant quality review process is in place**

288

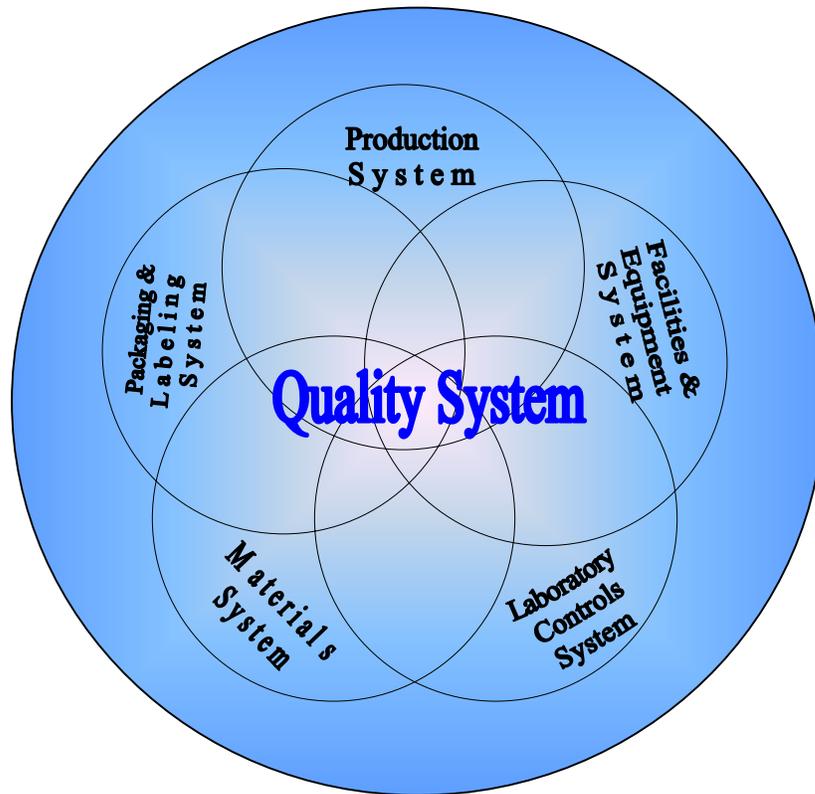
⁴ Generally, the term *quality unit* is used in this guidance. However, *quality control unit* is used when directly quoting **Parts** 210 and 211.

⁵ See Reference #1, comment 91.

288 **H. Six-system Inspection Model**

289 The FDA's Drug Manufacturing Inspection Compliance Program, which constitutes instructions
290 to FDA personnel for conducting inspections, is a systems-based approach for inspections and is
291 very consistent with the robust quality systems model presented in this guidance.⁶ The diagram
292 below shows the relationship among the six systems: the quality system and the five
293 **operational** systems. The quality system provides the foundation for the **operational**
294 systems that are linked **to**, and function within, it. The quality systems model described in this guidance
295 does not treat the five **operational** systems as discrete entities, but instead integrates them into
296 appropriate sections of the model. Those familiar with the six-system inspection approach will
297 see organizational differences in this guidance; however, the inter-relationship should be readily
298 apparent. One of the important themes of the systems based inspection compliance program is to
299 be able to assess whether each of the systems is in a state of control. The quality system model
300 presented in this guidance **should also help** firms achieve the desired state of control.

301 **FIG. 2 - SIX-SYSTEM INSPECTION APPROACH**



⁶ See Reference #2; this inspectional approach is currently in use by CDER and CBER for blood and blood product inspections. CBER and CVM are developing a similar approach for drug product inspections.

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IV. THE QUALITY SYSTEMS MODEL

321 The goal of this section is to describe a model for use in pharmaceutical manufacturing that can
322 help achieve compliance with CGMP regulations. It should be noted that implementing an
323 effective quality system in a manufacturing organization **may** require significant costs in time
324 and resources. However, the long-term benefits of implementing a quality system **should**
325 outweigh the costs

326 This section describes a robust quality systems model, which, if **properly** implemented, can
327 provide the controls needed to consistently produce a product of **more than** acceptable quality.
328 Where applicable, the relationship between elements of this model and CGMP regulations is
329 noted. At the end of each section, a table shows how the specific CGMP regulations correlate to
330 the elements in the quality systems model. As already explained, many of the quality systems
331 elements correlate closely with the CGMP regulations. It is important to emphasize that this
332 guidance is not recommending new regulatory requirements. The guidance is intended to
333 provide recommendations to manufacturers who are implementing, or plan to implement, a
334 quality systems model to help them comply with CGMP regulations. FDA regulatory and
335 inspectional coverage will remain focused on the specific CGMP regulations.

336 The model is organized into four major sections:

- 337 • Management Responsibilities
- 338 • Resources
- 339 • Manufacturing Operations
- 340 • Evaluation Activities

341 Under each of these sections, the specific elements of a **robust quality** systems model are
342 described. When elements of the quality systems model correlate with specific CGMP
343 regulations, this correlation is noted.

A. Management Responsibilities

345 **Today's** robust quality systems models call for management to play a key role in the design,
346 implementation, and management of the quality system. For example, management is
347 responsible for establishing the quality systems structure appropriate for the specific
348 organization. Management **also** has **the** ultimate responsibility to provide the leadership needed
349 for the successful functioning of the quality system. This section describes management's role in
350 developing, implementing, and managing a robust quality system. There is little overlap with the
351 CGMP regulations in this section (see the table at the end of the section).

1. Provide Leadership

353 In a **robust quality** system, senior management demonstrates commitment to developing and
354 maintaining their quality system. Leadership is demonstrated by aligning quality system plans
355 with the manufacturer's strategic plans to ensure that the quality system supports the

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356 manufacturer's mission and strategies. Senior managers set implementation priorities and
357 **oversee the development of** action plans. **These** managers can **also** provide support **to** the
358 quality system by:

- 359 • Actively participating in system design, implementation, and monitoring, including
360 system review (see IV.A.5.)
- 361 • Advocating continual improvement of operations and the quality system
- 362 • Committing necessary resources

363 In a robust quality systems environment, managers should demonstrate strong and visible
364 support for **their firm's global** quality system. **Managers should have an understanding**
365 **of all applicable regulations (US, other country and international)** and **apply that**
366 **insight to ensure the appropriate** global implementation **of their firm's quality system**
367 throughout the organization (e.g., across multiple sites).

368 Managers should also encourage internal communication on quality issues at all levels in the
369 organization. Communication should be ongoing among research and development, regulatory
370 affairs, manufacturing, and quality unit personnel on issues that affect quality, with management
371 included whenever appropriate.

372 *2. Structure the Organization*

373 When designing a robust quality system, management has the responsibility to determine the
374 structure of the organization and ensure that assigned authorities and responsibilities support the
375 production, quality, and management activities needed to produce quality products.
376 **Management has** the responsibility to ensure that the organization's structure **is**
377 **appropriately** documented. **In this regard, all responsibilities and authorities should be**
378 **documented (e.g., job descriptions and organization charts).**

379 Managers have the responsibility to communicate employee roles, responsibilities, and
380 authorities within the system and ensure that interactions are defined and understood.
381 **Managers are also responsible for ensuring that the documented procedures match**
382 **actual practice and that all who report to them are properly trained and follow all**
383 **applicable procedures.**

384 An organization also has the responsibility to give the individual who is appointed to manage the
385 quality system the authority to detect problems and effect solutions. Usually, a senior manager
386 administers the quality system and can, thus, ensure that the organization receives prompt
387 feedback on quality issues.

388 *3. Build Your Quality System to Meet Requirements*

389 Implementing a robust quality system can help ensure compliance with regulations related to
390 safety, identity, strength, quality, and purity as long as the quality system **meets or exceeds** the
391 **requirement minimums of the applicable** CGMP regulations as well as **meets** the **other**
392 needs of the **organization**. Under the quality systems model, the Agency recommends that

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393 senior managers ensure that the quality system **that is designed, approved and**
394 **implemented** provides clear organizational guidance and facilitates systematic evaluation of
395 issues. For example, according to the model, when documenting a quality system, the following
396 should be included.

- 397 • The scope of the quality system, including any outsourcing (see IV.B.4.)
- 398 • The standard of quality that will be used
- 399 • The manufacturer's **directives that** implement the quality systems criteria, and the
400 supporting objectives (see IV.A.4.)
- 401 • The procedures **and other documents** needed to establish and maintain the quality
402 system
- 403 • **The proofs that establish that the quality system meets the requirement**
404 **minimums of the applicable CGMP regulations**

405 It is recommended, under **a quality systems approach**, that a formal process be established to
406 **address requests for changes to all directives (e.g., mission, vision and values**
407 **statements, policies, plans, specifications, standard operating procedures, and work**
408 **instructions) covered by the firm's quality system.** It is also recommended that, when
409 operating under a quality system, manufacturers develop and **document control** procedures to
410 complete, secure, protect, and archive records, including data, which act as evidence of
411 operational and quality system activities. This approach is consistent with the CGMP
412 regulations, which require manufacturers to **establish and follow scientifically sound and**
413 **appropriate written** controls for specifications, plans, and procedures (**21 CFR Sec.**
414 **211.160**) that direct operational and quality system **operations**, and to ensure that these
415 directives are accurate, appropriately reviewed and approved, available for use, **and followed**
416 (see the CGMP **regulations** at §§ 211.22 (c) and (d), **211.80(a), 211.100(b), 211.110(a),**
417 **211.113(a) and (b), 211.122(a), 211.125(f), 211.130, 211.142, 211.150, 211.165(c),**
418 **211.166(a), and 211.167(a) – (c).**

419 *4. Establish Policies, Objectives, and Plans*

420 Under **a quality** system, policies, objectives, and plans provide the means by which senior
421 managers articulate their vision of quality to all levels of the organization.

422 It is expected that under a quality system senior management would incorporate a strong
423 commitment to quality into the organizational mission. Senior managers are expected to develop
424 an organizational quality policy that aligns with this mission; commit to meeting requirements
425 and improving the quality system; and propose objectives to fulfill the quality policy. Under a
426 quality system, to make the policy relevant, it must be communicated to, and understood by,
427 personnel and contractors (as applicable), and revised as needed.

428 Managers operating within a quality system are expected to define the quality objectives needed
429 to implement the quality policy. Senior management is expected to ensure that the quality
430 objectives are created at the top level of the organization (and other levels as needed) through a
431 formal quality planning process. Objectives are typically aligned with the manufacturer's

432 strategic plans. A quality system seeks to ensure that managers support the objectives with
433 necessary resources and have measurable goals that are monitored regularly.

434 Under a quality system, managers would be expected to use quality planning to identify
435 resources and define methods to achieve the quality objectives. It is recommended that quality
436 plans be documented and communicated to personnel to ensure awareness of how their
437 operational activities are aligned with **the organization's** strategic and quality goals.

438 *5. Review the System*

439 System review is a key component in any robust quality system to ensure its continuing
440 suitability, adequacy, and effectiveness. Under a quality system, senior managers are expected
441 to conduct reviews of the whole quality system according to a planned schedule. Such a review
442 typically **includes an assessment** of the **incoming and in-process materials used to**
443 **produce the finished product, the product produced, and the process used** as well as
444 customer needs (in this section, *customer* is defined as the recipient of the product and the
445 product is the goods or services being provided). Under a quality system, the review should
446 consider at least the following:

- 447 • The appropriateness of the quality policy and objectives
- 448 • The results of audits and other assessments
- 449 • Customer feedback, including complaints
- 450 • The analysis of data trending results
- 451 • The status of actions to prevent a potential problem or **the recurrence of previous**
452 **problems**
- 453 • **The status of any** follow-up actions from previous management reviews
- 454 • Any changes in business practices or environment that may affect the quality system
455 (such as the volume or type of operations)
- 456 • Product characteristics meet **both the applicable CGMP minimums** and the **other**
457 **customers' needs**

458 When developing and implementing new quality systems, reviews should, **in general**, take
459 place more frequently than when the system has matured. Outside of scheduled reviews, the
460 quality system is typically included as a standing agenda item in general management meetings.

461 Review outcomes typically include:

- 462 • Improvements to the quality system and related quality processes
- 463 • Improvements to manufacturing processes and products
- 464 • Realignment of resources

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465 Under a **CGMP-compliant** quality system, the results of a management review **must** be
466 recorded. Planned actions should be implemented using effective corrective and preventive
467 action and change control procedures.

468 **6. Audit Operations to Ensure Compliance**

469 Though often overlooked, system audit is a key component of any robust quality
470 system. Management is responsible for not only overseeing the auditing all
471 operations to ensure that all controls are being adhered to but also for ensuring that
472 all personnel are properly trained and procedure compliant. In their capacity as
473 self auditors, all personnel are responsible for operating in conformance to systems'
474 documentation as well as identifying and reporting any gaps or deficiencies in the
475 existing systems' documentation or any areas where the existing procedures need to
476 be or can be improved. In their capacity as peers, all personnel are responsible for
477 auditing their peers' compliance to all the applicable requirements of the
478 manufacturer's quality system. For those registered to some recognized quality
479 standard, the registering firm's auditors are also responsible for auditing the
480 registered manufacturer's adherence to the recognized Quality System standard as
481 well as all the requirements of the firm's quality system, including management.

482 The following table shows how the CGMP regulations correlate to specific elements in the
483 quality systems model for this section. Manufacturers, **processors, and packers** should
484 always refer to the specific regulations to ensure that they are complying with all regulations
485 **that apply to their firm.**

21 CFR CGMP Regulations Related to Management Responsibilities	
Quality System Element	Regulatory Citations
1. Leadership	—
2. Structure	Establish quality function: § 211.22 (a) (see definition in § 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) and 211.100(a)
5. System Review	Record review: § 211.180(e) 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)

486 **B. Resources**

487 Appropriate allocation of resources is key to creating a robust quality system and to complying
488 with the CGMP regulations. This section discusses the role of resources in developing,
489 implementing, and managing a robust quality system that fully complies with the **applicable**
490 CGMP regulations.

491 1. *General Arrangements*

492 Under a robust quality system, there should be sufficient allocation of resources for quality
493 system and operational activities. Under the model, senior management, or a designee, is
494 responsible for providing adequate resources for the following:

- 495 • To supply and maintain the appropriate facilities and equipment to consistently
496 manufacture a quality product **in compliance with the applicable CGMP (see §§ 211**
497 **Subparts C and D)**
- 498 • To acquire and receive materials, **including labeling, that meet or exceed their**
499 **applicable established CGMP minimums and** are suitable for their intended
500 purpose **(see §§ 211 Subpart E and 211.122)**
- 501 • For processing the materials **in a CGMP-compliant manner** to produce the finished
502 drug product **(see §§ 211 Subpart F)**
- 503 • **For packaging and labeling the finished drug product into finished packaged**
504 **drug product (see §§ 211 Subpart G and 211.160(b)(1))**
- 505 • For the **CGMP-compliant evaluation of an appropriate number representative**
506 **samples of incoming (see §§ 211.84(d), 211.87, 211.94(d), 211.122(a) and**
507 **211.160(b)(1), in-process materials (see §§ 211.110 and 211.160(b)(2)), and the**
508 **finished drug product (see §§ 211.160(b)(3), 211.165, 211.166 and 211.167),**
509 **including the collection, storage, and examination of representative samples of**
510 **incoming materials (see § 211.160(b)(1)), in-process materials (see §**
511 **211.160(b)(2)), stability samples (see §§ 211.160(b)(3) and 211.166), reserve**
512 **samples (see § 211.170), and, where required to meet the requirements in 21**
513 **CFR Sec. 211.198, complaint samples**
- 514 • **For the CGMP-compliant acceptance or rejection for release of each batch or**
515 **lot of drug product (see § 211.165) using representative sample evaluations**
516 **(see § 211.160(b)(3)) and statistical quality control (see § 211.165(d))**

517 2. *Develop Personnel*

518 Under a quality system, senior management is expected to support a problem-solving and
519 communicative organizational culture. Managers are expected to encourage communication by
520 creating an environment that values employee suggestions and acts on suggestions for
521 improvement. Management is also expected to develop cross-**functional** groups to share ideas
522 to improve procedures and processes.

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523 In the quality system, it is recommended that personnel be qualified to do the operations that are
524 assigned to them in accordance with the nature of, and potential risk to quality presented by, their
525 operational activities. Under a quality system, managers are expected to define appropriate
526 qualifications for each position to help ensure individuals are assigned appropriate
527 responsibilities. Personnel should also understand the impact of their activities on the product
528 and the customer (this quality systems parameter is also found in the CGMP regulations, which
529 identify specific qualifications [i.e., education, training, and experience or any combination
530 thereof]; see §§ 211.25(a) & (b)).

531 Under a quality system, **continuing** training is critical to ensure that the employees remain
532 proficient in their operational functions and in their understanding of CGMP regulations (**see §**
533 **211.25(a)**). Typical quality systems training would address the policies, processes, procedures,
534 and written instructions related to operational activities, the product/service, the quality system,
535 and the desired work culture (e.g., team building, communication, change, behavior). Under a
536 quality system (and the CGMP regulations), training is expected to focus on both the employees'
537 specific job functions and the related CGMP regulatory requirements.

538 Under a quality system, managers are expected to establish training programs that include the
539 following:

- 540 • Evaluation of training needs
- 541 • Provision of training to satisfy these needs
- 542 • Evaluation of effectiveness of training
- 543 • Documentation of training and/or re-training

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

546 *3. Facilities and Equipment*

547 Under a quality system, the technical experts (e.g., engineers, development scientists), who have
548 an understanding of pharmaceutical science, risk factors, and manufacturing processes related to
549 the product, are responsible for **defining** specific facility and equipment requirements.

550 According to CGMP regulations, the QCU has the responsibility of reviewing and approving all
551 initial design criteria and procedures pertaining to facilities and equipment and any subsequent
552 changes (see § 211.22(c)). FDA can, as resources permit, provide a preoperational review of
553 manufacturing facilities.⁷

554 According to the CGMP regulations, equipment must be **appropriately located**, qualified,
555 calibrated, cleaned, maintained **and operated in a state of control** to prevent contamination
556 and mix-ups (§§ 211.63, 211.67 **and** 211.68). **[Note: The CGMP regulations require a higher**
557 **standard for calibration and maintenance than most generic quality system models.]** The CGMP
558 regulations place as much emphasis on process equipment as on testing equipment (**21 CFR**

⁷ See Reference #4.

559 211 Subpart D—Equipment), while the majority of quality systems focus more on testing
560 equipment.¹² However, the quality system in ISO/IEC 17025:1999, though titled,
561 “General Requirements for the Competence of Testing and Calibration
562 Laboratories” (Reference 14), provides a general quality system that matches the
563 needs of a pharmaceutical manufacturing operation in which controls, evaluations,
564 and numerical values are critical aspects of the system. It applies to any
565 organization that wants to assure its customers of precision, accuracy and
566 repeatability of results produced. Moreover, ISO/IEC 17025 explicitly addresses
567 facilities and equipment, calibration and maintenance, and all aspects of control
568 and measurement unlike most other quality systems.

569 4. *Control of Outsourced Operations and Suppliers of Materials*

570 When outsourcing, a second party is hired under a contract to perform the operational processes
571 that are part of a manufacturer’s inherent responsibilities. For example, a manufacturer may hire
572 another firm to package and label or perform CGMP regulation training. Quality systems call for
573 contracts (quality agreements) that clearly describe the materials or service, quality specifications
574 responsibilities, and communication mechanisms. In all cases, including purchased
575 materials, the CGMP regulations hold the QCU of the pharmaceutical
576 manufacturer responsible for ensuring the adherence to quality by the contracted
577 party be it material vendor or contract operator (see § Sec. 211.22).

578 Under a quality system, the product manufacturer ensures that the contracted firm is qualified
579 through an on-site audit and other means, as appropriate. The contracted firm’s
580 personnel should be adequately trained and monitored for performance according to their quality
581 system, and the contracted firm's and contracting manufacturer’s quality standards should not
582 materially conflict. It is critical in a quality system to ensure that the responsible senior
583 managers (or officers) for the contracting manufacturer understand the specific
584 requirements of the contract. However, under the CGMP requirements, the QCU is responsible
585 for approving or rejecting products or services provided under contract (see § 211.22(a)).

586 As the table on the following page illustrates, the CGMP regulations are consistent with the
587 elements of a quality system in many of the areas discussed in this section. However,
588 manufacturers, processors, and packers should always refer to the specific regulations to
589 ensure that they are complying with all of the CGMP and other regulations that apply to
590 their organization.

591 C. **Manufacturing Operations**

592 There is significant overlap between the elements of a quality system and the CGMP regulation
593 requirements for manufacturing operations. It is important to emphasize again that FDA’s
594 enforcement programs and inspectional coverage remain based on the CGMP regulations. When
595 quality system elements in this section do not correlate to the CGMP regulations, the guidance
596 makes recommendations to help facilitate compliance with the CGMP regulations. The language

¹² See, for example, Reference # 5.

597

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 and Suppliers of Materials	Consultants: § 211.34
	Outsourcing: § 211.22(a)
	Incoming materials § 211.84(d)(2) and (3)

598 in this section has been tailored to the pharmaceutical manufacturing environment.

599 *1. Design and Develop Product and Processes*

600 In a **quality** systems manufacturing environment, the significant characteristics of the product
 601 being manufactured should be defined, from design to delivery, and control should be exercised
 602 over all changes. Quality and manufacturing processes and procedures — and changes to them
 603 — should be defined, approved, and controlled (CGMP also requires this; see § 211.100). It is
 604 important to establish **the** responsibility for designing or changing products **with personnel**
 605 **who understand the manufacturer’s quality systems and the requirement**
 606 **minimums of the applicable CGMP regulations. If quality is to be truly built into a**
 607 **product, the “building in” process must start at the beginning of the product design**
 608 **phase. This is the case because adding quality later is more difficult and costly, and**
 609 **may be difficult to accomplish.** Documenting associated processes **should** ensure that all
 610 critical variables are identified **and, to the extent required, properly controlled.** This
 611 documentation **should include:**

- 612 • Resources and facilities needed
- 613 • Procedures to carry out the process
- 614 • Identification of the process owner who will maintain and update the process as
615 needed
- 616 • Identification and control of critical variables
- 617 • Quality control measures, necessary data collection, monitoring, and appropriate
618 controls for the product and process
- 619 • Any validation activities, including operating ranges and acceptance criteria

- 620
- Effects on related **processes**, functions, or personnel

621 As discussed under section “IV.A. Management,” above, the model calls for managers to ensure
622 that product specifications and process **parameters determined** by the appropriate technical
623 experts (e.g., engineers, development scientists) are **scientifically sound and appropriate**.
624 In the pharmaceutical environment, experts **should** have an understanding of **the applicable**
625 **CGMP minimums**, pharmaceutical science, risk factors, and manufacturing processes as well
626 as how variations in materials and processes can ultimately affect the finished **product and/or**
627 **the attainment of the CGMP minimums**. **One key CGMP minimum that must be**
628 **appropriately addressed in development is the requirement that each batch must be**
629 **formulated with the intent to provide not less than 100 percent of the labeled or**
630 **established amount of active ingredient (see § 211.101(a)).**

631

2. *Define and Control Inputs*

632 In **current** quality systems models, the term *input* refers to any material that goes into a final
633 product **or is used in the manufacture, processing, or packing of the final product**, no
634 matter whether the material is purchased by the manufacturer or produced by the manufacturer
635 for the purpose of processing. *Materials* can include items such as components (e.g.,
636 ingredients, process water, and gas), containers and closures, **labels and labeling, and all**
637 **packaging items and packing supplies**. A robust quality system will ensure that all inputs
638 to the manufacturing process are reliable because quality controls will have been established for
639 the receipt, production, storage, and use of all inputs.

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

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

653 **However, if the ROA option is pursued, at least one specific identity test is required**
654 **to be conducted on representative samples of each shipment of each lot (see 21 CFR**
655 **Sec. 211.84(d)(2) and 21 CFR Sec. 211.160(b)(1)). [Note: The USP's IDENTIFICATION**
656 **tests are, in general, not identity tests much less specific identity tests and, unless proven**
657 **to be specific identity tests, cannot be used to comply with 21 CFR Sec. 211.84(d)(2).] In**
658 **addition, to be used for acceptance in lieu of evaluation, the supplier's ROA must**
659 **reflect adequate controls for each process critical variable factor (including, for the**

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660 active pharmaceutical ingredients, the “as is” weight-percent purity) in the
661 manufacturing process or processes in which it is intended to be used and certify
662 that each lot was made in accordance with the applicable CGMP since, by
663 definition, drug components are drugs (see 21 U.S.C. Section 321(g)(1)(D)). As an
664 essential element of purchasing controls, it is recommended that data for acceptance and
665 rejection of materials be analyzed for information on supplier performance.¹³ In addition, the
666 manufacturer’s quality control unit is responsible for approving the tests and
667 specifications for all materials (see § 211.22(a)).

668 The quality systems approach also calls for the auditing of suppliers on a periodic basis. During
669 the audit, the manufacturer, or its contracted qualified agent, can observe the testing or
670 examinations conducted by the supplier to help determine the reliability of the supplier’s COA.
671 An audit should also include a systematic examination of the supplier’s quality system to ensure
672 that reliability is maintained. The FDA recommends that a combination approach be used (i.e.,
673 verifying the suppliers’ COA through analysis and audits of the supplier). If full analytical
674 testing is not done, the audit should cover the supplier’s analysis. [Note: The collection of
675 representative samples of each shipment of each lot for testing or examination and a specific
676 identity test on each sample collected for testing or examination are still required (see §
677 211.84(b) and § 211.84(d)(2)).]

678 Under a quality systems approach, there should be procedures to verify that materials are from
679 approved sources (for application and licensed products, certain sources are specified in the
680 submissions). Procedures should also be established to encompass the acceptance, use, or the
681 rejection and disposition of materials produced by the facility (e.g., purified water). Systems that
682 produce these in-house materials should be designed, maintained, qualified, and validated to
683 ensure the materials meet their acceptance criteria.

684 In addition, we recommend that changes to materials (e.g., specification, supplier, or materials
685 handling) be implemented through a change control system (changes require review and
686 approval by the quality control unit [see § 211.100(a)]). It is also important to have a system in
687 place to respond to changes in materials from suppliers so that necessary adjustments to the
688 process can be made and unintended consequences prevented.

689 *3. Perform, Monitor and Validate Operations*

690 The core purpose of implementing a CGMP-compliant quality systems approach is to enable a
691 manufacturer to more efficiently and effectively perform, monitor and validate operations (see
692 § 211.110(a)). The goal of establishing, adhering to, measuring, and documenting
693 specifications and process parameters is to objectively assess whether an operation is meeting its
694 design (and product performance) objectives. In a robust quality system, production and process
695 controls should be designed to ensure that the untested finished products have the identity,
696 strength, quality and purity they purport or are represented to possess (CGMP also requires this;
697 see § 211.100(a)).

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

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698 In a **quality** system, a design concept established during product development typically matures
699 into a commercial design after process experimentation and progressive modification. Areas of
700 process weakness should be identified, and factors that are influential on critical quality
701 attributes should receive increased scrutiny. (The FDA recommends that scale-up studies be
702 used to help demonstrate that a fundamentally sound *design* has been fully realized.) A
703 sufficiently robust manufacturing process should be in place prior to commercial production.
704 With proper design (see section “IV.C.1”), and reliable mechanisms to transfer process
705 knowledge from development to commercial production, a manufacturer should be able to
706 **initially validate a manufacturing, processing or packing process¹⁴ and, depending on**
707 **the process, use continuous verification, continual conformity assessment, and/or**
708 **the ongoing qualification of each batch or lot to confirm: a) the process is in control and**
709 **b) the product is consistently meeting its established specification targets.**

710 In a quality system, **the initial phases of** process validation provide **preliminary** proof,
711 through commercial batch manufacture, that the design of the process produces the intended
712 product quality. Sufficient testing data will provide essential information on performance of the
713 new process, as well as a mechanism for continuous improvement. **Equipment** with the
714 potential for continuous monitoring and control can further enhance this knowledge base.
715 Although initial commercial batches can provide evidence to support the validity and consistency
716 of the process,¹⁵ **ongoing production** should be addressed by the establishment of continuous
717 improvement mechanisms in the quality system.¹⁶ Thus, in accordance with the quality systems
718 approach, process validation is not a one-time event, but an activity that continues **for as long**
719 **as that process is used.**

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

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

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

- 732 • Process steps should be verified using a validated computer system or a second person.
733 Batch production records should be prepared contemporaneously with each phase of

¹⁴ See Reference #6.

¹⁵ 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.

¹⁶ See Reference #7, FDA Compliance Policy Guide 7132c.08 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval, updated 03-12-2004.

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734 production. Although time limits can be established when they are important to the
735 quality of the finished product (CGMP addresses this; see § 211.111), this does not
736 preclude the ability to establish production controls based on in-process parameters that
737 can be based on desired process endpoints measured using real time testing or monitoring
738 apparatus (e.g., blend until **homogeneously** mixed vs. blend for 10 minutes).

739 • Procedures should be in place to prevent objectionable microorganisms in finished
740 product that is not required to be sterile and to prevent microbial contamination of
741 finished products purported to be sterile (CGMP also requires this; see § 211.113)
742 Sterilization processes should be validated (CGMP also requires this; see § 211.113(b))
743 for sterile drugs.¹⁷

744 **Though part of the manufacturing process, the CGMP regulations for finished**
745 **pharmaceuticals explicitly separate the final evaluation of the each batch for its**
746 **acceptability for release for distribution from the other aspects of the quality**
747 **system. Under CGMP, an explicit set of requirements must be met before a batch**
748 **can be released (see §§ 211.165 and 211.167). Since the CGMP regulations**
749 **specifically require the use of *statistical quality control criteria* that include**
750 ***appropriate acceptance levels* and/or *appropriate rejection levels*, the *minimum***
751 **level of quality is that established by the *appropriate* use of *statistical quality***
752 ***control* (§ 211.165(d)) on the results obtained for each critical product quality factor**
753 **on a *batch-representative* set of samples (§ 211.160(b)(3)).**

754 **Thus, under CGMP, *batch-representative statistical quality control* based on the**
755 **critical quality characteristics of the *representative samples* evaluated is the**
756 **minimum level of quality that is acceptable for deciding whether or not a batch is**
757 ***acceptable for release for distribution*. Therefore, all CGMP-compliant quality**
758 **systems must meet, or exceed, the *statistical quality control criteria* for each critical**
759 **variable factor that must be evaluated.**

760 Pharmaceutical products must meet their specifications and manufacturing processes must
761 consistently meet their **critical** parameters. Under a quality system, selected data are used to
762 evaluate the quality of a process or product. In addition, data collection can provide a means to
763 encourage and analyze potential suggestions for improvement. A quality systems approach calls
764 for the manufacturer to develop procedures that monitor, measure, and analyze the operations
765 (including analytical methods and/or statistical techniques). Knowledge continues to accumulate
766 from development through the entire commercial life of the product. Significant unanticipated
767 variables should be detected by a well managed quality system and adjustments implemented.
768 Procedures should be revisited as needed to refine operational design based on new knowledge.
769 Process understanding increases with experience and helps identify the need for changes **that**
770 **can improve the process or the quality of the drug product**. When implementing data
771 collection procedures, consider the following:

772 • Are **the methods for the evaluation of representative samples and data**
773 **collection properly** documented?

¹⁷ See Reference # 8.

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- 774 • When in the **product's production cycle** will the data be collected?
- 775 • How and to whom will measurement and monitoring activities be assigned?
- 776 • When should analysis and evaluation (e.g. trending) of **the data collected** be
- 777 performed (see V.E.1.)?
- 778 • What records are needed?

779 **Current** quality system **approaches indicate** that change control is warranted when data
780 analysis or other information reveals an area needing improvement. Changes to an established
781 process should be controlled and documented to ensure that desired attributes for the finished
782 product will be met (CGMP also requires this; see § 211.100(a)).

783 Change control with regard to pharmaceuticals is addressed in more detail in the CGMP
784 **regulations**. When developing a process change, it is important to keep the process design and
785 scientific knowledge of the product in mind. When major design issues are encountered through
786 process experience, a firm may need to revisit the adequacy of the design of the manufacturing
787 facility (**see** § 211.42), the design of the manufacturing equipment (**see** § 211.63), the design of
788 the production and control procedures (**see** § 211.100), or the design of **the controls themselves**
789 (**see** § 211.160). When implementing a change, determining its effect should be based on
790 monitoring and evaluating those specific elements that, **based on the firm's understanding**
791 **of the process, may be affected**. This allows the steps taken to implement a change and the
792 effects of the change on the process to be considered systematically. Evaluating the effects of a
793 change can entail additional tests or examinations of subsequent batches (e.g., additional in-
794 process testing or additional stability studies).

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

797 Under a quality system, procedures should be in place to ensure the accuracy of test results. Test
798 results that are out of specification may be due to testing problems or manufacturing problems
799 and should be investigated.¹⁸ Invalidation of test results should be: **a) scientifically sound, b)**
800 **based on an analyst error, method weakness, or equipment failure established from**
801 **the critical evaluation (investigation) of all data, and c) justified. [Note: To facilitate the**
802 **critical evaluation of data, the manufacturer's laboratory and other evaluation operations**
803 **(in-house and contract) should establish systems that identifiably links the specific**
804 **equipment, materials, personnel, method execution steps, and other factors that may affect**
805 **outcomes to each result value generated to the result values found.]**

806 The Agency recommends that, upon the completion of manufacturing and to maintain quality,
807 the manufacturer should consider shipment **and storage** requirements to meet special handling
808 needs (in the case of pharmaceuticals, one example might be refrigeration).

809 Under a quality system, trends should be continually identified and evaluated. One way of
810 accomplishing this is the use of statistical process control. The information from trend analyses
811 can be used to continually monitor quality, identify potential variances before they become

¹⁸ See Reference #9

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812 problems, bolster data already collected for the annual review, and facilitate improvement
813 throughout the product life cycle. **Ongoing minimum *process capability*** assessment can serve
814 as a basis for **establishing that the process is still in a validated state as well as for**
815 **determining the need for changes that can result in process improvements and efficiency (see**
816 **IV.D.1.).**

817 **4. *Monitor Packaging and Labeling Processes***

818 Packaging and labeling controls, critical stages in the pharmaceutical manufacturing process, are
819 not specifically addressed in **most** quality systems models. Therefore, the Agency recommends
820 that manufacturers, **processors and packers** always refer to the packaging and labeling control
821 regulations **in 21 CFR 211 Subpart G for their quality systems guidance in these areas.**
822 In addition — and this *is* consistent with **current** quality systems — FDA recommends that, as
823 part of the design process, before commercial production, the controls for all processes within
824 the packaging and labeling system be planned and documented in written procedures. The
825 procedures should outline quality control activities and the responsible positions. Specifications
826 and controls for the packaging and labeling materials should also be determined before
827 commercial production. Distinct labels with discriminating features for different products, such
828 as a product marketed with different strengths, should be included to prevent mislabeling and
829 resulting recalls.

830 **5. *Assess Stability and Expiration Dating***

831 **Unlike most quality systems, the CGMP regulations explicitly address the**
832 **intertwined quality issues of expiration dating and stability evaluation. To**
833 **establish a viable expiration date (see § 211.137), the stability of the drug product**
834 **must be evaluated (see § 211.166). Moreover, the ongoing assessment of stability**
835 **should, at a minimum, be an adjunct to the ‘annual review’ process (see § 180(e)).**
836 **Moreover, the stability evaluation must test a statistically valid number of batch**
837 **representative samples (§ 211.160(b)(3)) for each critical quality characteristic at**
838 **suitable intervals (see § 211.166(a)(1)).**

839 **6. *Address Nonconformities***

840 A key component in any quality system is handling nonconformities and/or deviations. The
841 investigation, conclusion, and follow-up should be documented (CGMP also requires this; see 21
842 CFR § 211.192). To ensure that a product conforms to requirements and expectations, it is
843 important to **assess the uniformity of the process and the product by evaluating**
844 **critical process parameters and critical product characteristics (e.g., specified control**
845 **parameters [such as, pH, hardness, viscosity, and disintegration time], and critical**
846 **product characteristics [such as, uniformity of content, drug release, and strength]) as**
847 **planned. Discrepancies may be detected during any stage of the process by an employee or a**
848 **validated computerized system designed to detect discrepancies, or during quality**
849 **control activities. Not all discrepancies will result in product defects; however, it is important to**
850 **document and handle them appropriately. A discrepancy investigation process is critical when a**
851 **discrepancy is found that affects product quality (CGMP also requires this; see § 211.192).**

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852 In a quality system, it is critical to develop and document procedures to define responsibilities
853 for halting and resuming operations, recording the nonconformity, investigating the discrepancy,
854 and taking remedial action. The corrected product or process should also be re-examined for
855 conformance and assessed for the significance of the nonconformity (CGMP also requires this;
856 see § 211.115).

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

861 Under a quality system, if a product or process does not meet requirements and has not been
862 released for use, it is essential to identify or segregate it so that it is not distributed to the
863 customer by accident. Remedial action may include correcting the nonconformity; or, with
864 proper authorization and documentation, allowing the product to proceed, or, if allowable,
865 using the product for another application; or rejecting the product. If an individual product that
866 does not meet requirements has been released, the Agency must be notified
867 “immediately”¹⁹ and the product should be recalled. Customer complaints should be handled
868 as discrepancies and be investigated (CGMP addresses this; see § 211.198).

869 *7. Improve Processes*

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

880 As the table on the following page illustrates, the CGMP regulations are consistent
881 with the elements of a quality system in many of the areas discussed in this section.
882 However, manufacturers, processors, and packers should always refer to the specific
883 regulations and their requirements to ensure that they are complying with all of the
884 CGMP and other regulations that apply to any aspect of their production
885 operations.
886

¹⁹ See 21 CFR Part 7

886

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. Define and Control Inputs	Materials: §§ 210.3(b), 211.80 – 211.94, 211.101, 211.122 and 211.125
3. Perform, Monitor and Validate Operations	Production: §§ 211.100, 211.103, 211.110, 211.111 and 211.113
	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. Assess Stability and Expiration Dating	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. Improve Processes	QC involvement: §§ 211.22(a), 211.115(b) and 211.160(a)

887

888 **D. Evaluation Activities**

889 As in the previous section, the elements of a quality system correlate closely with the
890 requirements in the CGMP regulations. See the table at the end of the section for the specifics.

891 *1. Analyze Data for Trends*

892 Quality systems call for continually monitoring trends and improving systems. This can be
893 achieved by monitoring data and information, identifying and resolving problems, and
894 anticipating and preventing problems.

895 Quality systems procedures involve collecting data from monitoring, measurement, complaint
896 handling, or other activities, and tracking this data over time, as appropriate. Analysis of data
897 can provide indications of the state of control of a process. The information generated may
898 be essential to achieving problem resolution or problem prevention (see IV.D.3.).

899 Although the minimum periodic review required in the CGMP regulations (see § 211.180(e))
900 calls for review of a representative number of initiated batches, released or not, of each
901 product along with a review of complaints, recalls, returned or salvaged drug
902 products, and investigations conducted under § 211.192 for each drug product on an
903 annual basis; quality systems calls for trending on a regular basis. Trending enables the
904 detection of potential problems as early as possible to plan corrective and preventive actions.
905 Another important concept of current quality systems is the use of trending to examine

906 processes as a **whole**. This **concept** is consistent with the annual review approach. These
907 trending analyses can help focus **the organization's** internal audits (see IV.D.2.).

908 2. *Conduct Internal Audits*

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

921 The quality systems model calls for managers who are responsible for the areas audited to take
922 timely action to resolve audit findings and ensure that follow-up actions are completed, verified,
923 and recorded. (FDA's policy is to not routinely review or copy reports and records that result
924 from internal audits per Compliance Policy Guide 130.300.⁹)

925 3. *Risk Assessment*

926 Effective decision-making in a quality systems environment is based on an informed
927 understanding of quality issues. Elements of risk should be considered relative to intended use,
928 and in the case of pharmaceuticals, patient safety and ensuring availability of medically
929 necessary drug products. Management should assign priorities to activities or actions based on
930 the consequences of action or inaction — otherwise known as *risk assessment*. It is important to
931 engage appropriate parties in assessing the consequences. Such parties include customers,
932 appropriate manufacturing personnel, and other stakeholders. Assessing consequences includes
933 using the manufacturer's risk assessment model to address risks, developing a strategy by
934 deciding which options to implement, taking actions to implement the strategy, and evaluating
935 the results. Since risk assessment is **an iterative** process, the assessment should be repeated if
936 new information is developed that changes the need for, or nature of, the risk **assessment**.

937 In a manufacturing quality systems environment, risk assessment is used as a tool in the
938 development of product specifications and critical process parameters. Used in conjunction with
939 process understanding, risk assessment helps manage and control change.

940 4. *Corrective Action*

941 Corrective action is a reactive tool for system improvement to ensure that significant problems
942 do not recur. Both quality systems and the CGMP regulations emphasize corrective actions.

⁹ See Reference #10.

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943 Quality systems approaches call for procedures to be developed and documented to ensure that
944 the need for action is evaluated relevant to the possible consequences, the root cause of the
945 problem is investigated, possible actions are determined, a selected action is taken within a
946 defined timeframe, and the effectiveness of the action taken is evaluated. It is essential to
947 maintain records of corrective actions taken (CGMP also requires this; see § 211.192).

948 It is essential to determine what actions are needed to prevent problem recurrence using
949 information from sources such as:

- 950 • Nonconformance reports and rejections
- 951 • Complaints
- 952 • Internal and external audits
- 953 • Data and risk analyses related to operations and quality system processes
- 954 • Management review decisions

955 5. *Preventive Action*

956 Being proactive is an essential tool in quality systems management. Tasks can include
957 succession planning, training, capturing institutional knowledge, and planning for personnel,
958 policy, and process changes.

959 A preventive action procedure will help ensure that potential problems and root causes are
960 identified, possible consequences assessed, and actions considered. The selected preventative
961 action should be evaluated and recorded, and the system should be monitored for the
962 effectiveness of the action. Problems can be anticipated and their occurrence prevented using
963 information from reviews of data and risk analyses associated with operational and quality
964 system processes, and by keeping abreast of changes in scientific and regulatory requirements.

965 6. *Promote Improvement*

966 **Management should improve the effectiveness and efficiency of the quality system itself**
967 **by appropriately adopting the applicable** quality activities described in this guidance.
968 Management may choose to use other improvement activities as appropriate. **However, it** is
969 critical that senior management be involved in the evaluation of this improvement process (see
970 section “IV.D.3.”). **In some organizations, the underlying purpose of the quality**
971 **management system is to continually drive improvement in all aspects of the firm’s**
972 **operations.**

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

- 977 • **Nonconformance reports and rejections**
- 978 • **Complaints**

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- 979 • Internal and external audits
- 980 • Data and risk analyses related to operations and quality system processes
- 981 • CAPA programs
- 982 • Management reviews

983 are used to guide the firm’s improvement plans and programs.

984 Other sources of improvement can be from lessons learned from unexpected
985 incidents and from the shared knowledge and experience of people in the
986 organization. Where possible, managers should create a culture of improvement
987 where people are encouraged to contribute improvement suggestions and to
988 participate in ongoing improvement activities. Setting improvement objectives as
989 part of the quality planning process, ensuring managers actively participate in a
990 coordinated program of system reviews, operating suggestion schemes, and
991 recognizing and rewarding improvement achievements are all senior-management
992 activities that may aid the establishment of a culture of improvement.

993 Prior to implementation, improvement actions should be addressed as the firm’s
994 change control procedures direct.

995 Finally, senior management should consider “best practices” benchmarking of the
996 operational practices of other organizations with the aim of improving their own
997 organization’s practices.

998 The following table shows how the CGMP regulations correlate to specific elements in the
999 quality systems model for this section. Manufacturers, processors, and packers should
1000 always refer to the specific regulations to ensure that they are complying with all of the
1001 CGMP and other regulations that apply to their organization.

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) and 211.192
5. Preventive Action	—
6. Promote Improvement	—

1002

1002

1003 **V. CONCLUSION**

1004 Implementation of a *comprehensive quality systems model* for human and veterinary
1005 pharmaceutical products, including biological products, will facilitate compliance with 21 CFR
1006 **Parts** 210 and 211. The central goal of a quality system is to ensure consistent production of
1007 safe and effective products and that these activities are **sustainable**. A robust quality system will
1008 promote process consistency by integrating effective knowledge-building mechanisms into daily
1009 operational decisions. Specifically, successful quality systems share the following characteristics,
1010 each of which **has** been discussed in detail above:

- 1011 • **Scientifically sound and appropriate** approaches
- 1012 • Decisions based on an understanding of the intended use of a product
- 1013 • Proper identification and control of areas of potential process weakness
- 1014 • Responsive deviation and investigation systems that lead to timely remediation
- 1015 • Sound methods for assessing **and reducing** risk
- 1016 • Well-defined processes and products, starting from development and extending
1017 throughout the **life of the process and the product it produces**
- 1018 • Systems for careful **analysis of the quality of incoming and in-process materials**
1019 **and the drug** product
- 1020 • Supportive management (philosophically and financially)

1021 Both good manufacturing practice and good business practice require a robust quality system.
1022 When fully developed and effectively managed, a quality system will lead to consistent,
1023 predictable processes that ensure that pharmaceuticals are safe, effective, and available for the
1024 consumer.

1025

1026

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1107

GLOSSARY

- 1107
- 1108 To gain a common understanding of a quality system as a whole, the following terms are used
1109 throughout the guidance.
- 1110 **Annual Review** - An evaluation, conducted at least annually, which assesses the quality
1111 standards of each drug product to determine the need for changes in drug product specifications
1112 or manufacturing or control procedures.
- 1113 **CAPA** – “Corrective **action** and preventive action”: A systematic approach **that** includes
1114 **procedures** needed to: correct (“correction”); prevent recurrence (“corrective action”); and
1115 eliminate the cause (“**preventive action**”) of nonconforming product and other quality
1116 problems. [**Adapted from 21 CFR § 820.100.**]
- 1117 **Continuous Improvement** – ongoing activities to evaluate and positively **modify** products,
1118 processes, and quality system to increase **process** effectiveness **and/or enhance product**
1119 **quality**.
- 1120 **Correction** - Repair, rework, or adjustment **relating** to the disposition of an existing
1121 discrepancy
- 1122 **Corrective Action** - Action taken to eliminate the causes of an existing non-conformity, defect
1123 or other undesirable situation to prevent recurrence.
- 1124 **Customer** – a person or organization (internal or external) that receives a product or service
1125 anywhere **in the “life cycle” of the product or service**.
- 1126 **Discrepancy** - Datum or result outside of the expected range, an unfulfilled requirement; may be
1127 called non-conformity, defect, deviation, out-of-specification, out-of-limit, out-of-trend, etc.
- 1128 **Metrics** - measurements taken over time that monitor, assess, and communicate vital information
1129 about the results of a process or activity. Metrics are generally quantitative, but can be
1130 qualitative.
- 1131 **Minimum Process Capability** – in general, the established specification range for a
1132 given quality characteristic divided by six times the uncertainty adjusted estimate
1133 of the standard deviation computed. In cases, like drug products, where the target
1134 value is not centered in the established specification range, a “*minimum process*
1135 *capability index*” approach should be used. Most commonly, the *minimum process*
1136 *capability index* is defined as a half-range divided by three times the uncertainty-
1137 adjusted estimate of the standard deviation computed. *Where the use of the*
1138 *capability index approach is appropriate for a drug product variable characteristic,*
1139 *the applicable half range is usually the predetermined upper specification limit*
1140 *minus the target value for the characteristic being evaluated.*

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- 1141 **Nonconformity** – a deficiency in a characteristic, product specification, process parameter,
1142 record, or procedure that renders the quality of a product unacceptable, indeterminate or not
1143 according to specified requirements.
- 1144 **Packaging Materials** – as used in the Packaging and Labeling System, excludes container and
1145 closures which are covered by 21 CFR 211 Subpart E (preamble comment # 312).
- 1146 **Pre-production** – drug development phase prior to pilot production.
- 1147 **Preventive Action** - Action taken to eliminate the cause of a potential non-conformity, defect, or
1148 other undesirable situation to prevent occurrence
- 1149 **Product/Service** – the intended results of activities or processes; products/services can be
1150 tangible or intangible.
- 1151 **Quality** – a measure of a product’s or a service’s **conformance to or divergence from** the
1152 customer’s stated or implied needs.
- 1153 **Quality Assurance** – **a system that addresses the** proactive and retrospective activities that
1154 provide confidence that requirements are fulfilled, **and the organizational unit with the**
1155 **primary responsibility for overseeing such activities.**
- 1156 **Quality Control** – **a system of verifying and maintaining a desired level of quality in**
1157 **a product, service or process by careful planning, use of proper equipment,**
1158 **continued inspection, and corrective action when required, and the organizational**
1159 **unit with the primary responsibility for overseeing such activities.**
- 1160 **Quality Management** – **the organization’s system for, and the personnel who are**
1161 **accountable for, the successful implementation of the firms’ quality system.”**
- 1162 **Quality Objectives** – specific measurable activities or processes to meet the intentions and
1163 directions as defined in the quality policy.
- 1164 **Quality Plan** – the documented result of quality planning that is disseminated to all relevant
1165 levels of the organization.
- 1166 **Quality Planning** – a management activity that sets quality objectives and defines the
1167 operational and/or quality system processes and the resources needed to fulfill the objectives.
- 1168 **Quality Policy** – a statement of intentions and direction issued by the highest level of the
1169 organization related to satisfying customers’ needs. It is similar to a strategic direction that
1170 communicates quality expectations that the organization is striving to achieve.
- 1171 **Quality System** – formalized business practices that define management responsibilities for
1172 organizational structure, processes, procedures and resources needed to fulfill product/service
1173 requirements, customer satisfaction, and continual improvement. In a CGMP regulatory context,
1174 the quality system establishes the foundation **that supports** the effective functioning of the
1175 **operational units that fall within the CGMP-compliant Quality System adopted.**

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 1176 **Quality Unit** – A group organized within an organization to promote quality in general practice.
- 1177 **Risk Assessment** - A systematic evaluation of the risk of a process by determining what can go
1178 wrong (risk identification), how likely is it to occur (risk estimation), and what the consequences
1179 are (**risk appraisal**).
- 1180 **Senior Management** – top management officials **and/or executive personnel** in a firm who
1181 have the authority and responsibility to **ensure that the firm has the resources and**
1182 **deploys them in a manner that guarantees its operations, systems, and products**
1183 **fully comply with the applicable statutes, CGMP regulations, and recognized**
1184 **standards**
- 1185 **Stakeholders** – an individual or organization having an ownership or interest in the delivery,
1186 results and metrics of the quality system framework or business process improvements.
- 1187 **Statistical Quality Control** – A tool of industrial management, comparable with
1188 *production control* and *cost control*, which uses the evaluation of *population*
1189 *representative evaluations* and *population statistics* to ensure manufacturing of a
1190 product produces a product that consistently meets its acceptance specifications for
1191 the finished product.