
Guidance for Industry

Process Validation: General Principles and Practices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 the Division of Dockets Management (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 Brian Hasselbalch or Grace McNally (CDER) 301-796-3286 or 301-796-3279, Christopher Joneckis (CBER) 301-827-0373, or Dennis Bensley (CVM) 301-827-6956.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

**November 2008
Current Good Manufacturing Practices (CGMP)**

Guidance for Industry Process Validation: General Principles and Practices

Additional copies are available from:

*Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Building 51, Room 2201
Silver Spring, MD 20993-0002
(Tel) 301-796-3400
<http://www.fda.gov/cder/guidance/index.htm>*

and/or

*Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
(Tel) 800-835-4709 or 301-827-1800
<http://www.fda.gov/cber/guidelines.htm>*

and/or

*Communications Staff, HFV-12
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place,
Rockville, MD 20855
(Tel) 240-276-9300
<http://www.fda.gov/cvm/guidance/published.htm>*

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)**

**November 2008
Current Good Manufacturing Practices (CGMP)**

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION.....	4
IV.	RECOMMENDATIONS.....	6
	A. General Considerations for Process Validation	6
	B. Specific Stages and Activities of Process Validation in the Product Lifecycle	6
	1. <i>Stage 1 – Process Design.....</i>	<i>7</i>
	2. <i>Stage 2 – Process Qualification.....</i>	<i>9</i>
	3. <i>Stage 3 – Continued Process Verification</i>	<i>13</i>
V.	CONCURRENT RELEASE OF PERFORMANCE QUALIFICATION BATCHES	14
VI.	DOCUMENTATION.....	15
VII.	ANALYTICAL METHODOLOGY.....	16

Guidance for Industry¹

Process Validation: General Principles and Practices

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance outlines the general principles and approaches that FDA considers to be appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (API or drug substance), collectively referred to in this guidance as *drugs* or *products*. This guidance incorporates principles and approaches that all manufacturers can use in validating a manufacturing process.

This guidance aligns process validation activities with the product lifecycle concept and with existing FDA guidance.² The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production. This guidance promotes modern manufacturing principles, process improvement, innovation, and sound science.

¹ This guidance has been prepared by the Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Center for Veterinary Medicine (CVM) at the Food and Drug Administration. FDA's Office of Regulatory Affairs (ORA) also contributed significantly to the development of this guidance.

² See the FDA/International Conference on Harmonisation (ICH) guidances for industry: Q8 Pharmaceutical Development, Q9 Quality Risk Management, and when finalized, Q10 Pharmaceutical Quality System (a notice of availability for the May 2007 ICH draft guidance, Q10 Pharmaceutical Quality System, published in the Federal Register on July 13, 2007 (72 FR 38604)). We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/cder/guidance/index.htm>, the CBER guidance page at <http://www.fda.gov/cber/guidelines.htm>, or the CVM guidance page at <http://www.fda.gov/cvm/Guidance/published.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

32 The following categories of drugs are within the scope of this guidance:

33

- 34 • Human drugs
- 35 • Veterinary drugs
- 36 • Biological and biotechnology products
- 37 • Finished products and active pharmaceutical ingredients (API or drug substance)³
- 38 • The drug constituent of a combination (drug and medical device) product

39

40 The following categories of products are not covered by this guidance:

41

- 42 • Type A medicated articles and medicated feed
- 43 • Medical devices
- 44 • Dietary supplements
- 45 • Human tissues intended for transplantation regulated under section 361 of the Public Health
- 46 Service Act⁴

47

48 This guidance does not specify what information should be included as part of a regulatory submission.
49 Interested persons can refer to the appropriate guidance or contact the appropriate Center in determining
50 what information should be included in a submission.

51

52 This guidance also does not specifically discuss the validation of automated process control systems
53 (i.e., computer hardware and software interfaces), which are commonly integrated into modern drug
54 manufacturing equipment. This guidance is relevant, however, to the validation of processes that
55 include automated equipment in processing.

56

57 FDA's guidance documents, including this guidance, do not establish legally enforceable
58 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
59 be viewed only as recommendations, unless specific regulatory or statutory requirements are
60 cited. The use of the word *should* in Agency guidances means that something is suggested or
61 recommended, but not required.

62

63 **II. BACKGROUND**

64

65 In the *Federal Register* of May 11, 1987 (52 FR 17638), FDA issued a notice announcing the
66 availability of a guidance entitled *Guideline on General Principles of Process Validation* (the

³ Separate current good manufacturing practice (CGMP) regulations for drug components such as APIs (drug substances) and intermediates have not published as of the date of this guidance, but these components are subject to the statutory CGMP requirements of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 351(a)(2)(B)). Process validation for APIs is discussed in the FDA/ICH guidance for industry, *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7A), available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>. Section XII of ICH Q7A describes in detail the principles to be followed in validating API processes.

⁴ See the FDA guidance for industry, *Validation of Procedures for Processing of Human Tissues Intended for Transplantation*, available on the Internet at <http://www.fda.gov/cber/guidelines.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

67 1987 guidance).⁵ Since then, we have obtained additional experience through our regulatory
68 oversight that allows us to update our recommendations to industry on this topic. This revised
69 guidance conveys FDA’s current thinking on process validation and is consistent with basic
70 principles first introduced in the 1987 guidance. This guidance also provides recommendations
71 that reflect some of the goals of FDA’s initiative entitled “Pharmaceutical CGMPs for the 21st
72 Century – A Risk-Based Approach,” particularly with regard to the use of technological
73 advances in pharmaceutical manufacturing, as well as implementation of modern risk
74 management and quality system tools and concepts. When finalized, this guidance will replace
75 the 1987 guidance.

76
77 FDA has the authority and responsibility to inspect and evaluate process validation performed by
78 manufacturers. The CGMP regulations for validating pharmaceutical (drug) manufacturing
79 require that drug products be produced with a high degree of assurance of meeting all the
80 attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)). Effective process
81 validation contributes significantly to assuring drug quality. The basic principle of quality
82 assurance is that a drug should be produced that is fit for its intended use; this principle
83 incorporates the understanding that the following conditions exist:

- 84
- 85 • Quality, safety, and efficacy are designed or *built* into the product.
- 86
- 87 • Quality cannot be adequately assured merely by in-process and finished-product
88 inspection or testing.
- 89
- 90 • Each step of a manufacturing process is controlled to assure that the finished product
91 meets all design characteristics and quality attributes including specifications.
- 92

93 For purposes of this guidance, ***process validation is defined as the collection and evaluation of***
94 ***data, from the process design stage throughout production, which establishes scientific***
95 ***evidence that a process is capable of consistently delivering quality products.*** Process
96 validation involves a series of activities taking place over the lifecycle of the product and
97 process. This guidance describes the process validation activities in three stages.

- 98
- 99 • Stage 1 – Process Design: The commercial process is defined during this stage based on
100 knowledge gained through development and scale-up activities.
- 101
- 102 • Stage 2 – Process Qualification: During this stage, the process design is confirmed as
103 being capable of reproducible commercial manufacturing.
- 104
- 105 • Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine
106 production that the process remains in a state of control.

⁵ The 1987 guidance was prepared by a working group that included representation from the Center for Devices and Radiological Health (CDRH). Since that time, CDRH elected to publish its own process validation guidance through the Global Harmonization Task Force. The principles and recommendations in that document, Quality Management Systems – Process Validation, edition 2 (available on the Internet at <http://www.ghhf.org/sg3/sg3-final.html>), are also useful to consider for drug manufacturing processes.

Contains Nonbinding Recommendations

Draft — Not for Implementation

107
108 This guidance describes activities typical in each stage, but in practice, some activities in
109 different stages might overlap.

110
111 *Before* any batch from the process is commercially distributed for use by consumers, a
112 manufacturer should have gained *a high degree of assurance* in the performance of the
113 manufacturing process such that it will consistently produce APIs and drug products meeting
114 those attributes relating to identity, strength, quality, purity, and potency. The assurance should
115 be obtained from objective information and data from laboratory-, pilot-, and/or commercial-
116 scale studies. Information and data should demonstrate that the commercial manufacturing
117 process is capable of consistently producing acceptable quality products within commercial
118 manufacturing conditions, including those conditions that pose a high risk of process failure.

119
120 A successful validation program depends upon information and knowledge from product and
121 process development. This knowledge and understanding is the basis for establishing an
122 approach to control that is appropriate for the manufacturing process. Manufacturers should:

- 123
- 124 • understand the sources of variation
 - 125 • detect the presence and degree of variation
 - 126 • understand the impact of variation on the process and ultimately on product attributes
 - 127 • control the variation in a manner commensurate with the risk it represents to the process
- 128 and product

129
130 Each manufacturer should judge whether it has gained sufficient understanding to provide a high
131 degree of assurance in its manufacturing process to justify commercial distribution of the
132 product. Focusing on qualification efforts without understanding the manufacturing process may
133 not lead to adequate assurance of quality. After establishing and confirming the process,
134 manufacturers must maintain the process in a state of control over the life of the process, even as
135 materials, equipment, production environment, personnel, and manufacturing procedures
136 change.⁶

137 138 **III. STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS** 139 **VALIDATION**

140
141 Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable
142 requirement under section 501(a)(2)(B) of the Act, which states the following:

143
144 A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the
145 facilities or controls used for, its manufacture, processing, packing, or holding do not
146 conform to or are not operated or administered in conformity with current good
147 manufacturing practice to assure that such drug meets the requirements of this Act as to

⁶ The statute and regulations described in section III of this guidance explain the requirement that the methods and facilities used for the manufacturing of drugs be operated and maintained under control sufficient to assure that the identity, strength, purity, and quality of a drug are as they purport or are represented to possess.

Contains Nonbinding Recommendations

Draft — Not for Implementation

148 safety and has the identity and strength, and meets the quality and purity characteristics,
149 which it purports or is represented to possess.

150
151 FDA regulations describing current good manufacturing practice (CGMP) are provided in 21
152 CFR parts 210 and 211.

153
154 Process validation is required, in both general and specific terms, by the CGMP regulations in
155 parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which
156 states that "[t]here shall be written procedures for production and process control *designed to*
157 *assure* that the drug products have the identity, strength, quality, and purity they purport or are
158 represented to possess" (emphasis added). This regulation requires that manufacturers design a
159 process including operations and controls that will result in a product meeting these attributes.
160 *Product quality* in the context of process validation means that product performance is consistent
161 from batch-to-batch and unit-to-unit. Many products are single-source or involve complicated
162 processes to manufacture. Validation also offers assurance that a process is reasonably
163 safeguarded from sources of variability affecting production output, the loss of which can cause
164 supply problems, thereby negatively affecting public health.

165
166 Other CGMP regulations define the various aspects of validation. Section 211.110(a), *Sampling*
167 *and testing of in-process materials and drug products*, requires that control procedures ". . . be
168 established to monitor the output and *to validate* the performance of those manufacturing
169 processes that may be responsible for causing variability in the characteristics of in-process
170 material and the drug product" (emphasis added). This regulation establishes the requirement
171 that even well-designed processes must include in-process control procedures to assure final
172 product quality.

173
174 CGMP regulations require that batch samples represent the batch under analysis (see, e.g., §
175 211.160(b)(3)) and that the sampling plan result in statistical confidence (§ 211.165(c) and (d))
176 that the batch meets its predetermined specifications (§ 211.165(a)). Section 211.110(b)
177 provides two principles to follow when establishing in-process specifications. The first principle
178 is that ". . . in-process specifications for such characteristics [of in-process material and the drug
179 product] shall be consistent with drug product final specifications . . ." Accordingly, in-process
180 material should be controlled to assure that the final drug product will meet its quality
181 requirements. The second principle in this regulation further requires that in-process
182 specifications ". . . shall be derived from previous acceptable process average and process
183 variability estimates where possible and determined by the application of suitable statistical
184 procedures where appropriate." This requirement, in part, establishes the need for manufacturers
185 to analyze process performance and control batch-to-batch variability.⁷
186

⁷ In the *Federal Register* of September 29, 1978 (43 FR 45013 at 45052), FDA published a final rule on "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding" (available on the Internet at <http://www.fda.gov/cder/dmpq/preamble.txt>). In the preamble of the final rule, the Agency further explains this principle.

Contains Nonbinding Recommendations

Draft — Not for Implementation

187 The CGMP regulations also describe and define activities connected with process design,
188 development, and maintenance. Section 211.180(e) requires that information and data about
189 product performance and manufacturing experience be periodically reviewed to determine
190 whether any changes to the established process are warranted. Ongoing feedback about product
191 performance is an essential feature of process maintenance.

192
193 In addition, the CGMP regulations require that facilities in which drugs are manufactured be of
194 suitable size, construction, and location to facilitate proper operations (21 CFR 211.42).
195 Equipment must be of appropriate design, adequate size, and suitably located to facilitate
196 operations for its intended use (21 CFR 211.63). Automated, mechanical, and electronic
197 equipment must be calibrated, inspected, or checked according to a written program designed to
198 assure proper performance (21 CFR 211.68).

199
200 In summary, the CGMP regulations require that manufacturing processes be designed and
201 controlled to assure that in-process materials and the finished product meet predetermined
202 quality requirements and do so consistently and reliably.

IV. RECOMMENDATIONS

A. General Considerations for Process Validation

207
208 In all stages of the product lifecycle, good project management and good archiving that capture
209 scientific knowledge will make the process validation program more effective and efficient.
210 These practices should ensure uniform collection and assessment of information about the
211 process, reduce the chance for redundant information gathering and analysis, and enhance the
212 accessibility of such information later in the product lifecycle.

213
214 We recommend an integrated⁸ team approach to process validation that includes expertise from a
215 variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry,
216 microbiology, statistics, manufacturing, and quality assurance. Project plans, along with the full
217 support of senior management, are essential elements for success.

218
219 Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate,
220 or confirm information about the product and process. All studies should be planned and
221 conducted according to sound scientific principles, appropriately documented, and should be
222 approved in accordance with the established procedure appropriate for the stage of the lifecycle.

B. Specific Stages and Activities of Process Validation in the Product Lifecycle

224
225
226 The following subsections describe the recommended stages and specific activities.
227

⁸ This concept is discussed in more detail in FDA's guidance for industry, *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*, available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

228 1. *Stage 1 – Process Design*

229
230 a. Building and Capturing Process Knowledge and Understanding

231
232 Process design is the activity of defining the commercial manufacturing process that will
233 be reflected in the master production and control records. The goal of this stage is to
234 design a process suitable for routine commercial manufacturing that can consistently
235 deliver a product that meets its critical quality attributes.

236
237 Generally, early process design experiments do not need to be performed under CGMP
238 conditions. They should, however, be conducted in accordance with sound scientific
239 methods and principles, including good documentation practices. This recommendation
240 is consistent with ICH guidance for industry, *Q10 Pharmaceutical Quality System*.⁹
241 Decisions and justification of the controls should be sufficiently documented and
242 internally reviewed to verify and preserve their value for use later in the lifecycle of the
243 process and product.

244
245 There are exceptions, however. For example, viral and impurity clearance studies have a
246 direct impact on drug safety and should be performed under CGMP conditions, even
247 when performed at small scale. The quality unit should be involved with these studies as
248 is typical during commercial production.

249
250 Product-development activities provide key inputs to the design stage, such as the
251 intended dosage form, the quality attributes, and a general manufacturing pathway.
252 Process information available from the product-development stage can be leveraged in
253 the process-design stage. However, the full spectrum of input variability typical of
254 commercial production is not generally known at this stage. The functionality and
255 limitations of commercial manufacturing equipment should be considered, as well as the
256 contributions of variability by different component lots, production operators,
257 environmental conditions, and measurement systems in the production setting.
258 Laboratory or pilot-scale models designed to be representative of the commercial process
259 can be used to estimate variability. However, it is not a regulatory expectation that the
260 process be developed and tested until it fails, but rather that a process be controlled
261 within commercial manufacturing conditions, including those combinations of conditions
262 posing a high risk of process failure.

263
264 Designing an efficient process with an effective process control approach is dependent on
265 the process knowledge and understanding obtained. Design of Experiment (DOE)
266 studies can help develop process knowledge by revealing relationships, including
267 multifactorial interactions, between the variable inputs (e.g., component¹⁰ characteristics

⁹ A notice of availability for this draft ICH guidance published in the *Federal Register* on July 13, 2007 (72 FR 38604). When finalized, this guidance will represent FDA’s current thinking on this topic.

¹⁰ “*Component* means any ingredient [raw material] intended for use in the manufacture of a drug product, including those that may not appear in such drug product” (21 CFR 210.3(b)(3)).

Contains Nonbinding Recommendations

Draft — Not for Implementation

268 or processing parameters) and the resulting outputs (e.g., in-process material,
269 intermediates, or the final product). Risk analysis tools can be used to screen potential
270 variables for DOE studies to minimize the total number of experiments conducted while
271 maximizing knowledge gained. The results of DOE studies can provide justification for
272 establishing ranges of incoming component quality, equipment parameters, and in-
273 process material quality attributes.

274
275 Other activities, such as experiments or demonstrations at laboratory or pilot scale, allow
276 evaluation of certain conditions and prediction of performance of the commercial
277 process. These activities also provide information that can be used to model or simulate
278 the commercial process. Computer-based or virtual simulations of certain unit operations
279 or dynamics can provide process understanding and avoid problems at commercial scale.
280 It is important to understand the degree to which models represent the commercial
281 process, including any differences that might exist, as this may have an impact on the
282 relevance of information derived from the studies.

283
284 It is essential that activities and studies resulting in product understanding be
285 documented. Documentation should reflect the basis for decisions made about the
286 process. For example, manufacturers should document the variables studied for a unit
287 operation and the rationale for those variables identified as significant. This information
288 is useful during the process qualification and continued process verification stages,
289 including when the design is revised or the strategy for control is refined or changed.

290
291 b. Establishing a Strategy for Process Control

292
293 Process knowledge and understanding is the basis for establishing an approach to process
294 control for each unit operation and the process overall. Strategies for process control can
295 be designed to reduce input variation, adjust for input variation during manufacturing
296 (and so reduce its impact on the output), or combine both approaches.

297
298 Process controls address variability to assure quality of the product. Controls can consist
299 of material analysis and equipment monitoring at significant processing points designed
300 to assure that the operation remains on target and in control with respect to output quality.
301 Special attention to control of the process through operational limits and in-process
302 monitoring is essential (1) where the product attribute is not readily measurable due to
303 limitations of sampling or detectability (e.g., viral clearance or microbial contamination),
304 or (2) when intermediates and products cannot be highly characterized and well-defined
305 quality attributes cannot be identified. These controls are included in the master
306 production and control records (see 21 CFR 211.186(a) and (b)(9)).

307
308 More advanced strategies, such as process analytical technology (PAT), use timely
309 analysis and control loops to adjust the processing conditions so that the output remains
310 constant. Manufacturing systems of this type can provide a higher degree of process
311 control. In the case of PAT strategy, the approach to process qualification will be
312 different from that for other process designs. Further information on PAT processes can

Contains Nonbinding Recommendations

Draft — Not for Implementation

313 be found in FDA’s guidance for industry on *PAT – A Framework for Innovative*
314 *Pharmaceutical Development, Manufacturing, and Quality Assurance* (available on the
315 Internet at <http://www.fda.gov/cder/guidance/index.htm>).
316

317 The planned commercial production and control records, which contain the operational
318 limits and overall strategy for process control, should be carried forward to the next stage
319 for confirmation.

320 321 2. *Stage 2 – Process Qualification*

322
323 During the process qualification stage of process validation, the process design is
324 confirmed as being capable of reproducible commercial manufacture. This stage has two
325 elements: (1) design of the facility and qualification of the equipment and utilities, and
326 (2) performance qualification (PQ). During this stage, CGMP-compliant procedures
327 must be followed and successful completion of this stage is necessary before commercial
328 distribution.¹¹ Products manufactured during this stage, if acceptable, can be released.

329 330 a. Design of a Facility and Qualification of Utilities and Equipment

331
332 Proper design of a manufacturing facility is required under 21 CFR part 211, subpart C,
333 of the CGMP regulations on *Buildings and Facilities*. It is essential that activities
334 performed to assure proper facility design and commissioning precede PQ. Activities
335 undertaken to demonstrate that utilities and pieces of equipment are suitable for their
336 intended use and perform properly is referred to in this guidance as *qualification*. These
337 activities necessarily precede manufacturing products at the commercial scale.

338
339 Qualification of utilities and equipment generally includes the following activities:

- 340
- 341 • Selecting utilities and equipment construction materials, operating principles, and
342 performance characteristics based on whether they are appropriate for their specific
343 use.
 - 344
 - 345 • Verifying that utility systems and equipment are built and installed in compliance
346 with the design specifications (e.g., built as designed with proper materials, capacity,
347 and functions, and properly connected and calibrated).
 - 348
 - 349 • Verifying that the utility system and equipment operate in accordance with the
350 process requirements in all anticipated operating ranges. This should include
351 challenging the equipment or system functions while under load comparable to that
352 expected during routine production. It should also include the performance of
353 interventions, stoppage, and start-up as is expected during routine production.

¹¹ As discussed in section III of this guidance, process validation (including process qualification) is legally enforceable under section 501(a)(2)(B) of the Act. FDA regulations require that process validation procedures be established and followed (21 CFR 211.100) before a batch can be distributed (21 CFR 211.22 and 211.165).

Contains Nonbinding Recommendations

Draft — Not for Implementation

354 Operating ranges should be shown capable of being held as long as would be
355 necessary during routine production.

356
357 Qualification of utilities and equipment can be covered under individual plans or as part
358 of an overall project plan. The plan should consider the requirements of use and can
359 incorporate risk management to prioritize certain activities and to identify a level of effort
360 in both the performance and documentation of qualification activities. The plan should
361 identify (1) the studies or tests to use, (2) the criteria appropriate to assess outcomes, (3)
362 the timing of qualification activities, (4) responsibilities, and (5) the procedures for
363 documenting and approving the qualification. It should also include the firm's
364 requirements for the evaluation of changes. Qualification activities should be
365 documented and summarized in a report with conclusions that address criteria in the plan.
366 The quality control unit must review and approve the qualification plan and report (21
367 CFR 211.22).

b. Performance Qualification Approach

368
369
370
371 The PQ is the second element of stage 2, process qualification. The PQ combines the
372 actual facility, utilities, equipment (each now qualified), and the trained personnel with
373 the commercial manufacturing process, control procedures, and components to produce
374 commercial batches. A successful PQ will confirm the process design and demonstrate
375 that the commercial manufacturing process performs as expected.

376
377 Success at this stage signals an important milestone in the product lifecycle and needs to
378 be completed before a manufacturer commences commercial distribution of the drug
379 product.¹² The decision to begin commercial distribution should be supported by data
380 from commercial batches. Data from laboratory and pilot studies can provide additional
381 assurance.

382
383 The approach to PQ should be based on sound science and the manufacturer's overall
384 level of product and process understanding. The cumulative data from all relevant
385 studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be
386 used to establish the manufacturing conditions in the PQ. For example, to have sufficient
387 understanding of the commercial process, the manufacturer will need to consider the
388 effects of scale; however, it is not typically necessary to explore the entire operating
389 range at commercial scale if assurance can be provided by other data. Previous credible
390 experience with sufficiently similar products and processes can also be considered. In
391 addition, we strongly recommend firms employ objective measures (e.g., statistical
392 metrics), wherever feasible and meaningful to achieve adequate assurance.

393
394 In most cases, PQ will have a higher level of sampling, additional testing, and greater
395 scrutiny of process performance. The level of monitoring and testing should be sufficient
396 to confirm uniform product quality throughout the batch during processing. This greater

¹² See section III of this guidance, Statutory and Regulatory Requirements for Process Validation.

Contains Nonbinding Recommendations

Draft — Not for Implementation

397 scrutiny accompanied by a higher level of sampling should continue through the process
398 verification stage, as appropriate.

399
400 The extent to which some materials, such as column resins or molecular filtration media,
401 can be re-used without adversely affecting product quality can be assessed in relevant
402 laboratory studies, and their usable lifetime should be confirmed by an ongoing PQ
403 protocol during commercial manufacture.

404
405 A manufacturing process that uses PAT may warrant a different PQ approach. Such a
406 process is one that is designed to measure in real time the attributes of an in-process
407 material and then adjust the process in a timely control loop so the process maintains the
408 desired quality of the output material. The process design stage and the process
409 qualification stage should have as a focus the measurement system and control loop.
410 Regardless, the goal remains the same: establishing scientific evidence that the process is
411 reproducible and will consistently deliver quality products.

c. Performance Qualification Protocol

412
413
414
415 A written protocol that specifies the manufacturing conditions, controls, testing, and
416 expected outcomes is essential for this stage of process validation. We recommend that
417 the protocol discuss:

- 418
419 • The manufacturing conditions including operating parameters, processing limits, and
420 component (raw material) inputs.
 - 421
422 • The data to be collected and when and how it will be evaluated.
 - 423
424 • Tests to be performed (in-process, release, characterization) and acceptance criteria
425 for each significant processing step.
 - 426
427 • The sampling plan including sampling points, number of samples, and the frequency
428 of sampling for each unit operation and attribute. The number of samples should be
429 adequate to provide sufficient statistical confidence of quality both within a batch and
430 between batches. The confidence level selected can be based on risk analysis as it
431 relates to the particular attribute under examination. Sampling during this stage
432 should be more extensive than is typical during routine production.
 - 433
434 • Criteria that provide for a rational conclusion of whether the process consistently
435 produces quality products. The criteria should include:
 - 436
437 ○ A description of the statistical methods to be used in analyzing all collected
438 data (e.g., statistical metrics defining both intra-batch and inter-batch
439 variability).
- 440

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 441 ○ Provision for addressing deviations from expected conditions and handling of
442 nonconforming data. Data should not be excluded from further consideration
443 in terms of PQ without a documented, science-based justification.
444
- 445 • Design of facilities and the qualification of utilities and equipment, personnel training
446 and qualification, and verification of material sources (components and
447 container/closures), if not previously accomplished.
448
 - 449 • Status of the validation of analytical methods used in measuring the process, in-
450 process materials, and the product.
451
 - 452 • Review and approval by appropriate departments and the quality unit.
453

d. Protocol Execution and Report

454
455
456 Protocol execution should not begin until the protocol has been reviewed and approved
457 by all appropriate departments, including the quality unit. Departure from the established
458 protocol must be made according to established procedure or provisions in the protocol.
459 Such departures must be justified and approved by all appropriate departments and the
460 quality unit before implementation (§ 211.100).
461

462 The commercial manufacturing process and routine procedures must be followed (§§
463 211.100(b) and 211.110(a)). The PQ lots should be manufactured under normal
464 conditions by personnel expected to routinely perform each step of each unit operation in
465 the process. Normal operating conditions should cover the utility systems (e.g., air
466 handling and water purification), material, personnel, environment, and manufacturing
467 procedures.
468

469 A report documenting and assessing adherence to the written protocol should be prepared
470 in a timely manner after the completion of the protocol. This report should:

- 471
- 472 • Discuss and cross-reference all aspects of the protocol.
473
- 474 • Summarize data collected and analyze the data, as specified by the protocol.
475
- 476 • Evaluate any unexpected observations and additional data not specified in the
477 protocol.
478
- 479 • Summarize and discuss all manufacturing nonconformances such as deviations,
480 aberrant test results, or other information that has bearing on the validity of process.
481
- 482 • Describe in sufficient detail any corrective actions or changes that should be made to
483 existing procedures and controls.
484

Contains Nonbinding Recommendations

Draft — Not for Implementation

- 485
- 486
- 487
- 488
- 489
- 490
- 491
- 492
- State a clear conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is considered to be in a sufficient state of control. If not, the report should state what should be accomplished before such a conclusion can be reached. This conclusion should be based on a documented justification for the approval of the process, and release of lots produced by it to the market in consideration of the entire compilation of knowledge and information gained from the design stage through the process qualification stage.
 - Include all appropriate department and quality unit review and approvals.

493

494

3. *Stage 3 – Continued Process Verification*

495

496

497 The goal of the third validation stage is to continually assure that the process remains in a
498 state of control (the validated state) during commercial manufacture. A system or
499 systems for detecting unplanned departures from the process as designed is essential to
500 accomplish this goal. Adherence to the CGMP requirements, specifically including the
501 collection and evaluation of information and data about the performance of the process
502 (see below), will allow detection of process *drift*. The evaluation should determine
503 whether action must be taken to prevent the process from drifting out of control (§
504 211.180(e)).

505

506 An ongoing program to collect and analyze product and process data that relate to
507 product quality must be established (§ 211.180(e)). The data collected should include
508 relevant process trends and quality of incoming materials or components, in-process
509 material, and finished products. The data should be statistically trended and reviewed by
510 trained personnel. The information collected should verify that the critical quality
511 attributes are being controlled throughout the process.

512

513 We recommend that a statistician or person with adequate training in statistical process
514 control techniques develop the data collection plan and statistical methods and
515 procedures used in measuring and evaluating process stability and process capability.
516 Procedures should describe how trending and calculations are to be performed.
517 Procedures should guard against overreaction to individual events as well as against
518 failure to detect process drift. Production data should be collected to evaluate process
519 stability and capability. The quality unit should review this information. If done
520 properly, these efforts can identify variability in the process and/or product; this
521 information can be used to alert the manufacturer that the process should be improved.

522

523 Good process design and development should anticipate significant sources of variability
524 and establish appropriate detection, control, and/or mitigation strategies, as well as
525 appropriate alert and action limits. However, a process is likely to encounter sources of
526 variation that were not previously detected or to which the process was not previously
527 exposed. Many tools and techniques, some statistical and others more qualitative, can be
528 used to detect variation, characterize it, and determine the root cause. We recommend
529 that the manufacturer use quantitative, statistical methods whenever feasible. We also

Contains Nonbinding Recommendations

Draft — Not for Implementation

530 recommend that it scrutinize intra-batch as well as inter-batch variation as part of a
531 comprehensive *continued process verification* program.

532
533 We recommend continued monitoring and/or sampling at the level established during the
534 process qualification stage until sufficient data is available to generate significant
535 variability estimates. Once the variability is known, sampling and/or monitoring should
536 be adjusted to a statistically appropriate and representative level. Process variability
537 should be periodically assessed and sampling and/or monitoring adjusted accordingly.

538
539 Variation can also be detected by the timely assessment of defect complaints, out-of-
540 specification findings, process deviation reports, process yield variations, batch records,
541 incoming raw material records, and adverse event reports. Production line operators and
542 quality unit staff should be encouraged to provide feedback on process performance.
543 Operator errors should also be tracked to measure the quality of the training program; to
544 identify operator performance issues; and to look for potential batch record, procedural,
545 and/or process improvements that could help to reduce operator error. We recommend
546 that the quality unit meet periodically with production staff to evaluate data, discuss
547 possible trends or drifts in the process, and coordinate any correction or follow-up actions
548 by production.

549
550 Data gathered during this stage might suggest ways to improve and/or optimize the
551 process by altering some aspect of the process or product such as the operating conditions
552 (ranges and set-points), process controls, component, or in-process material
553 characteristics. A description of the planned change, a well-justified rationale for the
554 change, an implementation plan, and quality unit approval before implementation must
555 be documented (21 CFR 211.100). Depending on the significance to product quality,
556 modifications may warrant performing additional process design and process
557 qualification activities.¹³

558
559 Maintenance of the facility, utilities, and equipment is another important aspect of
560 ensuring that a process remains in control. Once established, qualification status must be
561 maintained through routine monitoring, maintenance, and calibration procedures and
562 schedules (21 CFR part 211, subparts C and D). The data should be assessed periodically
563 to determine whether re-qualification should be performed and the extent of that re-
564 qualification. Maintenance and calibration frequency should be adjusted based on
565 feedback from these activities.

V. CONCURRENT RELEASE OF PERFORMANCE QUALIFICATION BATCHES

567
568
569 In most cases, the PQ protocol needs to be completed before the commercial distribution of a
570 product. In special situations, the PQ protocol can be designed to release a PQ batch for

¹³ Certain manufacturing changes may call for a formal notification to the Agency before implementation, as directed by existing regulations and *filing* guidance (i.e., documents that describe procedures for filing information to an application).

Contains Nonbinding Recommendations

Draft — Not for Implementation

571 distribution before completion of the protocol. The conclusions about the manufacturing
572 process should be made when the protocol is completed and the data is fully evaluated.

573
574 FDA expects that concurrent release will be used rarely. Concurrent release might be
575 appropriate for processes used infrequently because of limited demand for the product (e.g.,
576 orphan drugs), processes with necessarily low production volume per batch (e.g.,
577 radiopharmaceuticals, including positron emission tomography drugs), and processes
578 manufacturing *medically necessary* drugs to alleviate a short supply, which should be
579 coordinated with the Agency.

580
581 When warranted and used, concurrent release should be accompanied by a system for careful
582 oversight of the distributed batch to facilitate rapid customer feedback. For example, customer
583 complaints and defect reports should be rapidly assessed to determine root cause and whether the
584 process should be improved or changed. We recommend that each batch in a concurrent release
585 program also undergo stability testing and that this test data be promptly evaluated to ensure
586 rapid detection and correction of any problems.

587 588 **VI. DOCUMENTATION**

589
590 Documentation at each stage of the process validation lifecycle is essential for effective
591 communication in complex, lengthy, and multidisciplinary projects. Documentation is important
592 so that knowledge gained about a product and process is accessible and comprehensible to others
593 involved in each stage of the lifecycle. In addition to being a fundamental tenet of following the
594 scientific method, information transparency and accessibility are essential so that organizational
595 units responsible and accountable for the process can make informed, science-based decisions
596 that ultimately support the release of a product to commerce.

597
598 The degree and type of documentation required by CGMP is greatest during stage 2, process
599 qualification, and stage 3, continued process verification. Studies during these stages must
600 conform to CGMPs and must be approved by the quality unit in accordance with the regulations
601 (see 21 CFR 211.22 and 211.100). Viral and impurity clearance studies, even when performed at
602 small scale, also require full quality unit oversight as is necessary during routine commercial
603 production.

604
605 CGMP documents for commercial manufacturing (i.e., the initial commercial master batch
606 production and control record (21 CFR 211.186) and supporting procedures) are key outputs of
607 stage 1, process design. We recommend that firms diagram the process flow for the full-scale
608 process. Process flow diagrams should describe each unit operation, its placement in the overall
609 process, monitoring and control points, and the component, as well as other processing material
610 inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished
611 product). It is also useful to generate and preserve process flow diagrams of the various scales as
612 the process design progresses to facilitate comparison and decision making about their
613 comparability.

614

Contains Nonbinding Recommendations

Draft — Not for Implementation

615 **VII. ANALYTICAL METHODOLOGY**

616

617 Process knowledge is dependent on accurate and precise measuring techniques that are used to
618 test and examine the quality of drug components, in-process materials, and finished products.

619 For data to have value in predicting process outcomes, it is essential that the analytical tests be
620 scientifically sound (as required under 21 CFR 211.160). While validated analytical methods are
621 not required during product- and process-development activities, methods should be

622 scientifically sound (e.g., specific, sensitive, and accurate), suitable, and reliable for the specified
623 purpose. There should be assurance of proper equipment function for laboratory experiments.

624 Procedures for analytical method and equipment maintenance, documentation practices, and

625 calibration practices supporting process-development efforts should be documented or described.

626 Analytical methods supporting clinical supply production, particularly stage 2 and 3 studies,

627 must follow appropriate CGMPs in parts 210 and 211.

Contains Nonbinding Recommendations

Draft — Not for Implementation

REFERENCES

- 628
629
630 FDA, 1987 (CDER, CBER, and Center for Devices and Radiological Health (CDRH)),
631 *Guideline on General Principles of Process Validation*, guidance for industry, May 1987.
632
633 FDA, 2002 (CBER), *Validation of Procedures for Processing of Human Tissues Intended for*
634 *Transplantation*, guidance for industry, May 2002.
635
636 FDA, 2004 (CDER, CVM, and ORA), *PAT — A Framework for Innovative Pharmaceutical*
637 *Development, Manufacturing, and Quality Assurance*, guidance for industry, September
638 2004.
639
640 FDA, 2006 (CDER, CBER, CVM, and ORA), *Quality Systems Approach to Pharmaceutical*
641 *Current Good Manufacturing Practice Regulations*, guidance for industry, September
642 2006.
643
644 FDA/Global Harmonization Task Force (GHTF; medical devices), 2004, *Quality Management*
645 *Systems – Process Validation*, edition 2, guidance, January 2004.
646
647 FDA/ICH, 2001 (CDER and CBER), *Q7A Good Manufacturing Practice, Guidance for Active*
648 *Pharmaceutical Ingredients*, ICH guidance for industry, August 2001.
649
650 FDA/ICH, 2006 (CDER and CBER), *Q8A Pharmaceutical Development*, ICH guidance for
651 industry, May 2006.
652
653 FDA/ICH, 2006 (CDER and CBER), *Q9A Quality Risk Management*, ICH guidance for industry,
654 June 2006.
655
656 FDA/ICH (CDER and CBER) *Q10 Quality Systems*, ICH draft guidance for industry, May 2007
657 (when finalized, this guidance will convey FDA’s current thinking on this topic).