
Request for Quality Metrics Guidance for Industry

DRAFT GUIDANCE

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**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)**

July 2015
Pharmaceutical Quality/CMC
Current Good Manufacturing Practices (CGMPs)

Request for Quality Metrics Guidance for Industry

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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not create any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Quality metrics are used throughout the pharmaceutical industry to monitor quality control systems and processes and drive continuous improvement efforts in drug manufacturing. These metrics can also be used by FDA: to help develop compliance and inspection policies and practices, such as risk-based inspection scheduling of drug manufacturers; to improve the Agency’s ability to predict, and therefore, possibly mitigate, future drug shortages; and to encourage the pharmaceutical industry to implement state-of-the-art, innovative quality management systems for pharmaceutical manufacturing. This guidance includes an explanation of how the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) intend to collect data and use quality metrics to help ensure that their policies and practices continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry.

FDA understands that establishments involved in the manufacture, preparation, propagation, or processing of human drugs, including oversight to ensure quality,² currently use quality metrics as part of the process validation lifecycle and pharmaceutical quality system (PQS) assessment.³ This guidance outlines FDA’s authority to require owners and operators of such establishments to provide upon request records and information that FDA may inspect under section 704 of the Federal Food, Drug, and Cosmetic Act (FD&C Act, or the Act), and describes an initial set of requests the Agency intends to make to certain owners and operators. FDA intends to make its requests at the time this guidance is finalized, and to provide notice in the *Federal Register*. In order to receive public comment on these requests, this draft guidance describes the data that the

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² FDASIA section 711 added text to section 501 of the FD&C Act clarifying that, for the purposes of paragraph 501(a)(2)(B), the term “current good manufacturing practice” includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

³ Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1).

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37 Agency plans to request, the uses FDA intends to make of the requested data, and the quality
38 metrics that FDA intends to calculate.

39
40 Under Title VII of the Food and Drug Administration Safety and Innovation Act (FDASIA)
41 Public Law No. 112-144, FDA may require the submission of any records or other information
42 that FDA may inspect under section 704 of the FD&C Act, in advance or in lieu of an inspection,
43 by requesting the records or information from a person that owns or operates an establishment
44 that is engaged in the manufacture, preparation, propagation, compounding, or processing of a
45 drug.^{4,5}

46
47 Under this authority, FDA intends to request the submission of data from owners and operators
48 of certain human drug establishments that are subject to inspection under section 704 of the
49 FD&C Act. Except as noted below, FDA intends to request data from owners and operators of
50 establishments that are required to register under section 510 of the FD&C Act and that are
51 engaged in the manufacture, preparation, propagation, compounding, or processing of finished
52 dosage forms (FDF) of covered drug products or active pharmaceutical ingredients (API) used in
53 the manufacture of covered drug products. Covered drug products would include: drug products
54 that are the subject of an approved application under section 505 of the FD&C Act or under
55 section 351 of the PHS Act; products that can be marketed pursuant to an over-the-counter
56 (OTC) monograph; and marketed unapproved drug products.

57
58 The requests would not apply to: establishments that are not required to register under section
59 510 of the FD&C Act and regulations FDA has issued at 21 CFR 207.10; compounders operating
60 under section 503A or registered as outsourcing facilities under section 503B of the FD&C Act;
61 medical gas manufacturers; positron emission tomography manufacturers; and manufacturers of
62 blood and blood components for transfusion, vaccines, cell therapy products, gene therapy
63 products, allergenic extracts, human cells, tissues, and cellular and tissue based products and
64 non-recombinant versions of plasma derived products. Additional detail is provided below.

65
66 In addition, establishments that receive requests under section 704(a)(4) would be encouraged to
67 submit quality metrics data for certain foreign establishments that are not required to register, as
68 discussed below.

69
70 While FDA recognizes the value of quality metrics, we also recognize that individual data points
71 and metrics are not solely indicative of the state of quality of the establishment or products.
72 Rather, FDA intends to use quality metrics data in context with other sources of quality data, as
73 further described in this guidance.

⁴ See section 704(a)(4) of the FD&C Act. Such records or other information must, upon the request of FDA, be provided to FDA within a reasonable timeframe, within reasonable limits, and in a reasonable manner, and in either electronic or physical form, at the expense of such person. Any request shall include a sufficient description of the records requested. Upon receipt of the records requested, FDA must provide confirmation of receipt.

⁵ See also sections 262(c) and (j) of the Public Health Service Act (PHS) that authorize inspections for biologics and incorporate FD&C Act requirements by reference. See also sections 351(c) of the PHS Act (authorizing inspections for biologics) and section 351(j) of the PHS Act (providing that the FD&C Act applies to biological products, except that NDAs are not required for biologics approved under BLAs).

74
75 FDA intends to carefully review data submitted in response to its requests, to help inform
76 decisions about how to develop its program. FDA may add to, revise, or remove quality metrics
77 data from future quality metrics data requests to reflect our understanding of current
78 manufacturing and establishment considerations and the utility of the data the Agency has
79 received.

80
81

82 **II. BACKGROUND**

83

84 **A. Modernization of Regulatory Oversight of Drug Quality and Promotion of** 85 **Post-Approval Improvements**

86

87 FDA’s approach to quality oversight has evolved in recent years. CDER and CBER are
88 committed to supporting the modernization of pharmaceutical manufacturing as part of the
89 Agency’s mission to protect and promote public health. These efforts also may be one long-term
90 strategy to mitigate drug shortages by addressing underlying causes of shortages, as noted in
91 *FDA’s Strategic Plan for Preventing and Mitigating Drug Shortages*.⁶ In 2002, FDA launched
92 an initiative entitled “Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach,” to
93 encourage the implementation of a modern, risk-based pharmaceutical quality assessment
94 system.⁷ The initiative was published with several goals, including ensuring that regulatory
95 review, compliance, and inspection policies continue to support continuous improvement and
96 innovation in the pharmaceutical manufacturing industry. Since publication of the
97 *Pharmaceutical cGMPs for the 21st Century*, CDER has promoted a vision of “a maximally
98 efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products
99 without extensive regulatory oversight.”⁸

100

101 FDA used the following criteria to select the quality metrics that it intends to calculate using
102 requested data when this guidance is final: metrics should be (1) objective, (2) subject to
103 inspection under section 704 of the FD&C Act, and (3) valuable in assessing the overall state of
104 quality of the product and process, commitment to quality by the manufacturer, and the health
105 (i.e., effective functioning) of the associated PQS, while (4) avoiding any undue reporting
106 burden. These metrics are not intended to be an all-inclusive set of the quality metrics that FDA
107 could consider useful to assess a product and manufacturer’s state of quality. For example,
108 senior management commitment to quality is an important factor in evaluating the overall health
109 of the PQS and quality culture. While it may be difficult to measure this factor objectively
110 between different companies, the Agency is committed to a dialog with industry to consider

⁶ See *FDA’s Strategic Plan for Preventing and Mitigating Drug Shortages* at:
<http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf>.

⁷ See *Pharmaceutical cGMP’s for the 21st Century: A Risk-Based Approach* at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm>.

⁸ See *FDA Pharmaceutical Quality Oversight: One Quality Voice* at
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf>.

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111 benchmarks and standards that could provide acceptable metrics that specifically demonstrate
112 senior management’s commitment to a culture of quality (refer to Request for Comment on the
113 Additional Reporting of Optional Metrics - Optional Metrics Related to Quality Culture and
114 Process Capability/Performance, highlighted in section V.B). Also, while FDA has not selected
115 metrics based on data or information that are readily accessible to the Agency, such as number of
116 recalls, these data and information should also be part of manufacturers’ product- and
117 establishment-specific evaluations. FDA encourages manufacturers to routinely use additional
118 quality metrics beyond the metrics described in this guidance in performing these evaluations.
119

**B. Use of Quality Metrics by FDA for Risk-Based Inspection Scheduling and
Prediction of Drug Shortages**

120
121
122
123 The quality metrics program is expected to play an important role in addressing risk-based
124 inspection scheduling and in the prediction, and potential mitigation, of drug shortages. Section
125 510(h)(3) of the FD&C Act was amended by section 705 of FDASIA to require that FDA inspect
126 establishments that are required to register with FDA “that are engaged in the manufacture,
127 preparation, propagation, compounding, or processing of a drug or drugs in accordance with a
128 risk-based schedule established by” FDA. The provision replaced the requirement that FDA
129 conduct inspections of certain domestic drug establishments at least once every two years. Risk-
130 based scheduling helps FDA focus resources on facilities that present the greatest risk to
131 consumers.⁹
132

133 Section 510(h)(3) of the FD&C Act provides for a risk-based schedule of inspections for drugs
134 be established according to the known safety risks posed by establishments that are required to
135 register. These risks are based on certain factors as outlined in section 510(h)(4)(A-F): (1) the
136 compliance history of the establishment; (2) the record, history, and nature of recalls linked to
137 the establishment; (3) the inherent risk of the drug manufactured, prepared, propagated,
138 compounded, or processed at the establishment; (4) the inspection frequency and history of the
139 establishment, including whether the establishment has been inspected pursuant to section 704
140 within the last 4 years; (5) whether the establishment has been inspected by a foreign
141 government or agency of a foreign government recognized under section 809 of the FD&C Act;
142 and, (6) any other criteria that FDA deems necessary and appropriate for purposes of allocating
143 inspection resources. FDA intends to use quality metrics to support its understanding of the
144 inherent risk of manufacturing establishments and products and as the basis for criteria it deems
145 necessary and appropriate for purposes of allocating inspection resources.
146

147 In addition, shortages of drugs and biologics pose a significant public health threat, delaying, and
148 in some cases even denying, critically needed care for patients. Taking action to reduce drug
149 shortages remains a top priority for FDA. The Agency has found that the majority of drug
150 shortages stem from quality concerns—substandard manufacturing facilities or processes are
151 discovered, or significant quality defects are identified in finished product, necessitating

⁹ See, e.g., U.S. House, Committee on Energy & Commerce, Food and Drug Administration Reform Act of 2012 (H.R. Rep No. 112-495) Washington, Government Printing Office, 31.

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152 remediation efforts to fix the issue, which in turn, may interrupt production, and cause a shortage
153 of drugs.¹⁰

154
155 In order to both inform FDA’s risk-based drug inspection scheduling and to better detect
156 manufacturing conditions that may lead to a shortage, FDA intends to collect and use
157 quantitative quality data to calculate certain quality metrics, as further described in section V.
158 FDA intends to use these quality metrics, in part, as a tool to identify risk-based factors that
159 could increase or decrease inspection frequency and that could potentially be predictive of drug
160 supply disruption.

161
162 The collection of these data is also intended to help direct our inspections. In addition, FDA
163 intends to consider whether these metrics may provide a basis for FDA to use improved risk-
164 based principles to determine the appropriate reporting category for post-approval manufacturing
165 changes, with emphasis on encouraging lifecycle manufacturing improvement. However, if the
166 integrity or utility of the quality data submitted is found questionable based on FDA’s evaluation
167 of submitted data or other information, such as an on-site inspection, the uses to which we would
168 put the reported quality data would need to be re-evaluated, along with the nature of future
169 requests.

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171

172 **III. LEGAL AUTHORITY**

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176

**A. Records Associated with the Process Validation Lifecycle and PQS
Assessment**

177 Manufacturers are expected to use a quality program in order to support process validation, and
178 the metrics described in this guidance could be a part of such a program. Process validation
179 involves a series of activities taking place over the lifecycle of the product and process. Process
180 validation for drugs (finished pharmaceuticals and components) is a requirement under section
181 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)), which states the following:

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

189 FDA regulations describing current good manufacturing practice (CGMP) requirements for
190 finished pharmaceuticals are provided in 21 CFR parts 210 and 211, including the associated

¹⁰ In 2012, for example, based on information collected from manufacturers, FDA determined that 66 percent of disruptions in drug manufacturing were the result of either (1) efforts to address product-specific quality failures, or (2) broader efforts to remediate or improve an unsafe manufacturing facility. *FDA’s Strategic Plan for Preventing and Mitigating Drug Shortages*, see figure 2, at <http://www.fda.gov/downloads/drugs/drugsafety/drugshortages/ucm372566.pdf>.

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191 record-keeping requirements (21 CFR 211 subpart J). Process validation is required, in both
192 general and specific terms, by the CGMP regulations in parts 210 and 211, for example, 21 CFR
193 211.100(a) and 211.110(a).¹¹ As described in FDA’s process validation guidance, manufacturers
194 depend on information and knowledge from product and process development as the basis for
195 establishing an approach to control of the manufacturing process that result in products with the
196 desired quality attributes. Manufacturers should:

- 197
- 198 • Understand the sources of variation.
- 199
- 200 • Detect the presence and degree of variation.
- 201
- 202 • Understand the impact of variation on the process and ultimately on product
- 203 attributes.
- 204
- 205 • Control the variation in a manner commensurate with the risk it represents to the
- 206 process and product.
- 207

208 After establishing and confirming the process, manufacturers must maintain the process in a state
209 of control over the life of the process, even as materials, equipment, production environment,
210 personnel, and manufacturing procedures change.¹² Manufacturers should use ongoing programs
211 to collect and analyze product and process information to evaluate the state of control of the
212 process. These programs may identify process or product problems and opportunities for
213 manufacturing improvements that can be evaluated and implemented throughout the lifecycle.

214

215 CGMP regulations for human drugs require an ongoing program to maintain and evaluate
216 product and process data that relate to product quality.¹³ One means of performing this
217 assessment is the Annual Product Review (APR), which is conducted at least annually, in which
218 data collected includes relevant process trends and quality of incoming materials or components,
219 in-process materials, and finished products. The data should be statistically trended and
220 reviewed by trained personnel. The information collected should verify that the quality attributes
221 are being appropriately controlled throughout the process and determine if the specifications,
222 manufacturing, or control procedures should be updated or improved. This evaluation includes a
223 review of a representative number of batches and associated records and complaints, recalls,
224 returned or salvaged drug products, and investigations.¹⁴ Further, maintenance of the facility,
225 utilities, and equipment is another important aspect of ensuring that a process remains in

¹¹ Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1) for a description of other sections of 21 CFR Part 211 that set forth requirements related to aspects of process validation.

¹² FDASIA section 711 added text to section 501 of the FD&C Act clarifying that, for the purposes of paragraph 501(a)(2)(B), the term “current good manufacturing practice” includes the implementation of oversight and controls over the manufacture of drugs to ensure quality, including managing the risk of an establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

¹³ See 21 CFR 211.180(e).

¹⁴ The Product Quality Review of APIs is comparable to the Annual Product Review conducted for finished drug products under 21 CFR 211.180(e). Refer to FDA guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

226 control.¹⁵ The equipment and facility qualification data should be assessed periodically. In order
227 to perform this evaluation, reporting establishments and manufacturers should be calculating and
228 evaluating quality metrics on a continual basis. Some establishments may also choose to adopt
229 systems to internally calculate and evaluate metrics in real time.
230

231 **B. Authority to Inspect Records and Request Records in Advance of or In Lieu**
232 **of an Inspection**
233

234 Section 704(a)(4)(A) of the FD&C Act (added by FDASIA section 706, Records for Inspection)
235 authorizes FDA to request from a person that owns or operates an establishment that is engaged
236 in the manufacture, preparation, propagation, compounding, or processing of a drug, “in advance
237 of or in lieu of” an inspection, any records or other information that we may inspect under
238 section 704 of the FD&C Act, provided we request submission of the information “within a
239 reasonable timeframe, within reasonable limits, and in a reasonable manner.” We consider
240 FDA’s request for quality metrics data records or information to be “in advance of” an inspection
241 for purposes of section 704(a)(4)(A). FDA intends to request quality data to help FDA improve
242 its inspection-setting priorities, including informing a risk-based inspection schedule to satisfy
243 the requirement in section 510(h) of the FD&C Act. Additionally, FDA intends to use quality
244 metrics data it receives to assist staff in preparing for in-person inspections, to improve their
245 efficiency and effectiveness. Finally, at the Agency’s discretion, if quality metrics derived from
246 the data provide evidence of a lower risk of poor quality drugs and an acceptable commitment to
247 high quality drug manufacturing judged in light of other relevant risk information, the requests
248 may reduce the inspection frequency at an establishment.
249

250 Under section 501(j) (added by FDASIA section 707), a drug is deemed adulterated if it has been
251 manufactured, processed, packed, or held in a facility the owner of which delays, denies, or
252 limits an inspection, or refuses to permit entry or inspection.¹⁶ If an owner, operator, or agent of
253 a facility fails to produce records and information requested pursuant to section 704(a)(4) of the
254 FD&C Act within a reasonable timeframe, drugs from the facility may be deemed adulterated
255 under section 501 of the Act and subject to enforcement action. Additionally, refusal to permit
256 access to a record as required under section 704(a) of the FD&C Act is a prohibited act under
257 section 301(e) of the Act.
258
259

260 **IV. THE USE OF QUALITY METRICS AND EFFECTS OF NON-REPORTING**
261

262 **A. How FDA Intends to Use Quality Metrics**
263

264 FDA intends to use quality metrics data to further develop FDA’s risk-based inspection
265 scheduling, to identify situations in which there may be a risk for drug supply disruption, to
266 improve the efficiency and effectiveness of establishment inspections, and to improve FDA’s

¹⁵ See 21 CFR 211 subparts C and D.

¹⁶ For further information regarding 501(j), see FDA guidance for industry *Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection*.

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267 evaluation of drug manufacturing and control operations. FDA expects that the initial use of the
268 metrics will be to consider a decreased surveillance inspection frequency for certain
269 establishments. For example, establishments that have highly controlled manufacturing
270 processes have the potential to be inspected less often (as a lower priority for inspection) than
271 similar establishments that demonstrate uncontrolled processes (as a higher priority for
272 inspection). In addition, FDA intends to consider whether these metrics may provide a basis for
273 FDA to use improved risk-based principles to determine the appropriate reporting category for
274 post-approval manufacturing changes.

275
276 FDA intends to evaluate whether data reported by manufacturers is consistent with the Agency's
277 understanding of the specific quality data requested (e.g., definitions). In addition, we intend to
278 evaluate how best to interpret and use the metrics. For example, is it more meaningful to
279 compare metrics for different products within the same establishment, or for the same product
280 manufactured at different establishments, or as an establishment-specific trend over time? Is it
281 more appropriate to use certain metrics to compare all types of establishments (or a subset
282 making the same dosage form or same drug) against each other? What is the best way to
283 compare metrics for products that vary in manufacturing complexity (e.g., biotechnology and
284 biological products are often considered more complex to manufacture)?

285
286 FDA intends to carefully review data submitted in response to its requests, to help inform
287 decisions about additional quality metrics data requests the Agency may make in the future. We
288 may add to, revise, or remove quality metrics data from future requests to reflect our
289 understanding of current manufacturing and establishment considerations and the utility of the
290 data the Agency has received. We also intend to provide additional opportunity after our initial
291 requests are made for industry to provide feedback and additional comments, as well as share
292 knowledge from ongoing quality metrics programs.

293
294 FDA recognizes that any individual data point or quality metric is not solely indicative of the
295 state of quality of the establishment or products; rather, FDA intends to use this information in
296 context. For example, the use of new, in-line analytical technology used for real time release
297 testing with increased sensitivity might result in better detection of in-process out of
298 specification (OOS) results and a temporary increase in total OOS results. However, improved
299 detection that allows for the diversion and rejection of poor quality product will allow for
300 improved assurance of quality. FDA is sensitive to this possibility and continues to support and
301 encourage the use of modern manufacturing technology.

302
303 FDA also intends to use quality data collected under section 704(a)(4)(A) of the FD&C Act as
304 one factor in identifying establishments that may pose significant risks to consumers, such as
305 risks from unsafe products and drug shortages. Reported data and metrics, along with internal
306 FDA data (e.g., inspection results, recalls, Field Alert Reports, Biological Product Deviation
307 Reports) may indicate an ongoing product quality problem that requires correction. Evaluation
308 of this information will enable FDA to work with establishments towards early resolution of
309 quality problems and to reduce the likelihood that the establishment's operations will be
310 disrupted and impact the drug supply. FDA does not intend to publicly disclose quality metric
311 data submissions.

312
313 Manufacturers can expect that reported quality data may be verified during on-site inspections.
314 If inconsistencies are identified, the integrity of the report may be questioned and used as an
315 additional factor in FDA risk-based or for-cause inspection scheduling.
316

317 **B. Effects of Non-Reporting**
318

319 The failure to report requested quality data may elevate an establishment’s predicted risk in
320 FDA’s prioritization of inspections and may lead to an earlier inspection. In addition, products
321 associated with an establishment that does not report as required under section 704(a)(4)(A) may
322 be deemed adulterated under section 501 and subject to enforcement action.
323

324
325 **V. REPORTING OF QUALITY DATA AND CALCULATION OF QUALITY**
326 **METRICS**
327

328 In this section, we describe the set of requests for quality metrics data that FDA intends to make
329 and give notice of in the *Federal Register* at the time the guidance is finalized.
330

331 **A. Who Reports and Who May Contribute to the Report**
332

333 As described in section III of this guidance, owners or operators of establishments that are
334 engaged in the manufacture, preparation, propagation, compounding, or processing of a drug are
335 required to report data to FDA that the Agency may inspect under section of the FD&C Act,
336 upon the Agency’s request, in advance or in lieu of an inspection. At the time the guidance is
337 finalized, FDA intends to give notice in the *Federal Register* to certain owners and operators of
338 establishments subject to inspection under section 704 that they are requested to submit quality
339 metrics data.
340

341 **1. Establishments covered by the requests**
342

343 Except as noted below, FDA intends to request quality metrics data from owners and operators
344 of each establishment that is (1) required to register under with FDA under section 510, and (2)
345 engaged in the manufacture, preparation, propagation, compounding, or processing of the FDF of
346 a covered drug product, or an API used in the manufacture of a covered drug product. For
347 purposes of these requests, a covered drug product would mean a drug product that is:
348

- 349 ○ subject to an approved application under section 505 of the FD&C Act or under
350 section 351 of the PHS Act.
- 351
- 352 ○ marketed pursuant to an OTC monograph.
- 353
- 354 ○ a marketed unapproved drug product.

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355
356 The requests would include (but are not limited to) contract laboratories, contract sterilizers,
357 contract packagers, and other establishments, as appropriate, engaged in the manufacture,
358 preparation, propagation, compounding, or processing of the FDF or API for a covered drug. At
359 this time, these requests do not include excipient or container/closure manufacturers.

360
361 Additionally, the requests would not apply to persons and establishments that are not required to
362 register under section 510 of the Act and regulations FDA has issued at 21 CFR 207.10;
363 compounders operating under section 503A or registered as outsourcing facilities under section
364 503B of the FD&C Act; medical gas manufacturers, positron emission tomography
365 manufacturers, or manufacturers of blood and blood components for transfusion, vaccines, cell
366 therapy products, gene therapy products, allergenic extracts, human cells, tissues, and cellular
367 and tissue based products and non-recombinant versions of plasma derived products. For
368 purposes of this guidance, we will refer to the establishments whose owners or operators are
369 subject to FDA’s requests as “covered establishments.”

370
371 **2. Who reports for covered establishments**

372
373 FDA intends to ask industry to submit one report for each FDF and one report for each API of a
374 covered drug product, which includes quality metrics data from each covered establishment that
375 has the requested data. FDA believes that, as part of its responsibility for oversight and controls
376 over the manufacture of drugs to ensure quality, one establishment will already possess or have
377 access to all of the quality metrics data needed to submit such reports — for example, through
378 contract or because all of the covered establishments with quality metrics data related to a FDF
379 of a covered drug product or API used in the manufacture of a covered drug product will be
380 under common ownership or control.¹⁷ This establishment should combine the data so that a
381 single report is submitted for each FDF and each API. In this guidance, we refer to the
382 establishments that submit reports to FDA as “reporting establishments.”

383
384 FDA believes that the quality control unit (QCU)¹⁸ in each reporting establishment for an FDF or
385 API will generally be best positioned to compile reports for submission to FDA, given the unit’s
386 responsibilities and authorities for the oversight of drug products as described in 21 CFR 211.22.

387
388 FDA recognizes that there may be foreign establishments that are not required to register with
389 the Agency, but have quality metrics data relating to an FDF or API of a covered drug intended
390 for import to the United States. At this time, FDA does not intend to request the submission of
391 quality metrics data directly from such foreign establishments under section 704(a)(4). Instead,
392 covered establishments are encouraged to provide to reporting establishments any of the
393 requested quality metrics data they have or are able to obtain for such foreign establishments, so
394 that the data can be included in the reporting establishments’ submissions. The absence of data
395 for such establishments may elevate an establishment’s predicted risk in FDA’s risk-based
396 inspection scheduling and may increase the likelihood of an inspection. Conversely, reliable

¹⁷ See, e.g., FDASIA section 711; 21 CFR 200.10(b).

¹⁸ For the purpose of this guidance, the term “quality control unit” is synonymous with “quality unit.”

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397 data from such facilities may decrease an establishment’s predicted risk and reduce the
398 likelihood of an inspection. FDA intends to evaluate these submissions for information about the
399 state of manufacturing and product quality at these foreign establishments and to consider
400 whether to issue broader requests in the future.

401
402 As knowledge is gained through this initiative, FDA may consider quality data reporting for
403 additional human drug establishments subject to inspection under section 704 of the FD&C Act.
404

B. Quality Metrics that FDA Intends to Calculate

405
406
407 The following set of quality metrics that FDA intends to calculate based on industry reporting
408 was developed with stakeholder input. The metrics were identified as being objective, subject to
409 inspection under section 704 of the FD&C Act, and a valuable component in assessing the
410 overall effectiveness of a PQS, within reasonable limits, and in a reasonable manner, while
411 avoiding an undue reporting burden. FDA believes that these quality metrics, in conjunction
412 with other data accessible to FDA, provide important information about operational reliability
413 and quality culture. Additional, optional metrics, as described below, could provide further
414 detail about quality culture and process capability/performance. In this draft guidance, FDA
415 seeks comment on whether to include the option of submitting these metrics when the guidance
416 is final.

417
418 Using reported data described in the following section, FDA intends to calculate the following
419 quality metrics for each product and establishment, where applicable:

- 420
421 • **Lot Acceptance Rate** = $1 - x$ (x = the number of specification-related rejected lots in a
422 timeframe divided by the number of lots attempted by the same establishment in the same
423 timeframe).
- 424
425 • **Product Quality Complaint Rate** = the number of product quality complaints received
426 for the product divided by the total number of lots of the product released in the same
427 timeframe.
- 428
429 • **Invalidated Out-of-Specification (OOS) Rate** = the number of OOS¹⁹ test results for
430 the finished product invalidated by the establishment divided by the total number of OOS
431 test results divided by the total number of tests performed by the establishment in the
432 same timeframe.
- 433
434 • **Annual Product Review (APR) or Product Quality Review (PQR) on Time Rate** =
435 the number of APRs or PQRs completed within 30 days of annual due date at the
436 establishment divided by the number of products produced at the establishment.
- 437

¹⁹ Reference this guidance’s Glossary for out-of-specification result.

Additional Request for Comment

Optional Metrics Related to Quality Culture and Process Capability/Performance

FDA is requesting public comment on whether to give establishments the opportunity to submit additional, optional metrics as evidence of manufacturing robustness and a commitment to quality. Data from these optional metrics may merit a reduction in inspection frequency. In addition, FDA intends to consider whether these metrics may provide a basis for FDA to use improved risk-based principles to determine the appropriate reporting category for post-approval manufacturing changes, with emphasis on encouraging lifecycle manufacturing improvement. Comments are requested on the use of optional metrics, the submission of optional metrics, these three specific optional metrics, and any other optional metrics that should be considered.

Quality Culture

FDA acknowledges the importance of quality culture to the overall state of quality of the product, process, and commitment to quality. We also recognize that many companies measure quality culture and encourage this practice. FDA is proposing the following metrics for comment:

- **Senior Management Engagement:** A corporate commitment to quality has been identified in multiple public forums as a strong indicator of a robust PQS. FDA recognizes the difficulties in measuring senior management engagement and support of quality, including manufacturing and facility improvements. Proposed Optional Metric 1 is intended to identify whether senior management with the resources and authority to implement changes are engaged in the assessment of product quality, as well as whether there is shared knowledge of this assessment with the quality and manufacturing organizations. Comments are requested on Proposed Optional Metric 1 and alternative approaches.

Proposed Optional Metric 1:

Was each APR or PQR reviewed and approved by the following: (1) the head of the quality unit, (2) the head of the operations unit; (3) both; or (4) neither?²⁰

- **CAPA Effectiveness:** A comprehensive corrective action and preventive action program has been identified as a strong indicator of a robust quality culture. Continual improvement is based on preventing the initial occurrence (preventive action) or recurrence (corrective action) of a detected nonconformity or other undesirable situation. FDA has observed that less robust quality systems often rely on preventing recurrence solely through personnel re-training (i.e., the same training has already been provided to the employee(s)), while more robust quality systems consider re-design and re-development of the process. Comments are requested on proposed Optional Metric 2 and alternative approaches.

²⁰ See 21 CFR 211.22, 211.25(b), 211.180(e), 211.180(f), 211.192, 211.204, and 211.208.

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Proposed Optional Metric 2:

What percentage of your corrective actions involved re-training of personnel (i.e., a root cause of the deviation is lack of adequate training)?^{21,22}

Process Capability/Performance

FDA recognizes the importance of statistical process control as a tool in understanding and managing variability in both product and processing for application and non-application products.²³ We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed and should guard against overreaction to individual events as well as against failure to detect unintended process variability.²⁴ Frequently, however, manufacturing control elements are developed based upon early estimates of process capability at time of product launch or using control strategies considered appropriate at the time of approval. Knowledge gained during scale-up and commercial manufacturing can be useful in further developing the control strategy. It is important that statistical analysis be used to enable and advance product quality, not to inhibit continuous improvement and application of post-launch learning and experience to the assurance of high quality product and consistent processing. FDA requires manufacturers to apply statistical tools in a manner appropriate to assure that the product and process reproducibly meet specifications on an ongoing basis. Specifications must be meaningful in terms of achieving the desired finished product characteristics. This data enables science and risk-based quality risk management by identifying when manufacturing improvement is needed.²⁵

Proposed Optional Metric 3:

- A “yes” or “no” value of whether the establishment’s management calculated a process capability or performance index for each critical quality attribute (CQA) as part of that product’s APR or PQR.²⁶
- A “yes” or “no” value of whether the establishment’s management has a policy of requiring a corrective action or preventive action (CAPA) at some lower process capability or performance index.
- If “yes” to the above question – what is the process capability or performance index that triggers a CAPA? If “no” to the above question – please do not respond.

²¹ See 21 CFR 211.22, 211.100, 211.180(e), and 211.192.

²² Refer to FDA guidance for industry *Q10 Pharmaceutical Quality System*.

²³ One reference that may be useful is ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.

²⁴ Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1).

²⁵ See 21 CFR 211.110.

²⁶ See 21 CFR 211.22(c), 211.100, and 211.192.

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C. What Quality Data Would Be Reported

Section V.B describes each metric FDA intends to calculate and the associated data that would be used to calculate each metric. FDA encourages reporting establishments to report these data by product and establishment, where applicable, to support FDA’s calculation of the metrics described in section V.A.²⁷ The requests proposed in this draft guidance are for information that we could inspect under section 704 of the FD&C Act, and that we understand is developed and maintained in the course of manufacturing drugs in compliance with current good manufacturing practice. In general, the information needed to respond to FDA’s proposed requests is maintained in accordance with 21 CFR 211 subpart J and evaluated under 21 CFR 211.180(e). Additional references are provided to 21 CFR 211 for finished dosage forms. For non-finished dosage form products (e.g., APIs), refer to section 501(a)(2)(B) of the FD&C Act and FDA guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. FDA would ask for data to be aggregated and reported as described in section V in which is a readily accessible format.

- The number of lots attempted of the product.²⁸
- The number of specification-related rejected lots of the product, rejected during or after manufacturing.²⁹
- The number of attempted lots pending disposition for more than 30 days.³⁰
- The number of OOS results for the product, including stability testing.³¹
- The number of lot release and stability tests conducted for the product.³²
- The number of OOS results for lot release and stability tests for the product which are invalidated due to lab error.³³

²⁷ FDA expects that data associated with contract laboratories will be limited to the number of OOS results, the number of lot release and stability tests conducted, and the number of invalidated OOS.

²⁸ See 21 CFR 211.165, 211.188.

²⁹ See 21 CFR 211.192, 165(f).

³⁰ See 21 CFR 211.188. Under current good manufacturing practice, deviation investigations and final disposition decisions must be completed in a timely manner. Note that the request for lots pending disposition more than 30 days was selected as a measurement tool and not intended to clarify the timely manner in which disposition should be completed. Further, a lot may be subdivided or grouped after the first attempted lot is initiated. Each subsequent subdivision or grouping is considered a separate lot. These data will be used to verify data validity supporting the lot acceptance rate metric.

³¹ See 21 CFR 211.160(a). For the purpose of this guidance, this includes: (1) finished product and stability test results *only* and, (2) all finished product and stability test results that initially appear as OOS, even if invalidated by a subsequent laboratory investigation.

³² See 21 CFR 211.165, 211.194(a), and 610.1. If a lot release or stability test is conducted multiple times for a lot, each test should be counted.

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- The number of product quality complaints received for the product.³⁴
 - The number of lots attempted which are released for distribution or for the next stage of manufacturing the product.³⁵
 - If the associated APRs or PQRs were completed within 30 days of annual due date for the product.³⁶
 - The number of APRs or PQRs required for the product.³⁷

557 Reporting of data related to lots of drugs that are imported, intended for import into the United
558 States, or manufactured in the United States or its territories only is preferred. However, FDA
559 recognizes that it may not be possible for some covered establishments and reporting
560 establishments to identify attempted lots, rejected lots, and OOS results that are specific to drugs
561 that are imported, intended for import or manufactured in the United States. In this instance, if
562 the manufacturing process uses the same process and controls, data for lots that are not specific
563 to those that are imported, intended for import or manufactured in the United States could be
564 reported for the lot acceptance and invalidated OOS metrics. The selection of drugs that are
565 either: (1) imported, intended for import or manufactured in the United States, or (2) all drugs
566 using the same manufacturing process and controls which are not necessarily imported, intended
567 for import or manufactured in the United States, should remain consistent within and across
568 reporting cycles, unless otherwise specified. Product quality complaint and APR/PQR data
569 should be reported related to drugs that are imported, intended for import or manufactured in the
570 United States or its territories.

571

572 **D. How to Report Quality Data to FDA**

573

574 FDA intends to request that reporting establishments submit quality metrics data reports for a
575 one-year period that begins after the Agency issues its requests, as specified in the request.
576 Reports would be submitted within 60 days of the end date of the reporting period. For example,
577 if the requests called data for the period October 1, 2016 to September 30, 2017, data reports
578 would be due by December 1, 2017. We intend to request data segregated in the report on a
579 quarterly basis.

580

³³ See 21 CFR 211.160(a). While this guidance is requesting data specific to lot release and stability tests, FDA recognizes the importance of other types of testing (e.g., in-process testing, environmental testing, raw material and packaging component testing).

³⁴ See 21 CFR 211.165, 211.198. This quality data is the total number of all product quality complaints, as defined in the Glossary. This does not include multiple counting of the same product quality complaint if the complaint receiver forwards the complaint to individual manufacturers for further investigation.

³⁵ See 21 CFR 211.150(b).

³⁶ See 21 CFR 211.22(d); 211.180(e). The data for APRs and PQRs not completed within 30 days was selected as a measurement tool and not intended to clarify the timely manner in which APRs and PQRs should be completed.

³⁷ See 21 CFR 211.22; 211.180(e).

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581 Appendix A is a quality component list that describes the information that would be submitted to
582 FDA through the FDA Electronic Submissions Gateway (ESG). FDA intends to provide
583 additional technical details in a separate technical specification. Once FDA receives information
584 in response to requests under section 704(a)(4), the Agency intends to issue a confirmation of
585 receipt, in accordance with section 704(a)(4)(B) of the FD&C Act. Any optional metrics would
586 may be submitted using the same method described above. Information included in quality
587 metric data submissions should be submitted in English. FDA believes that segregating reports
588 by quarter and the submission through the ESG on the timetable provided is within reasonable
589 limits and in a reasonable manner.

590

591 Data that FDA would request varies by business segment/type and is described in Appendix A.

592

**Additional Request for Comment
Frequency of Quality Metrics Data Reporting**

593

594 At this time, FDA is considering when it should make additional requests for quality metrics
595 data. Comments are requested on whether to make requests annually or any other possible
596 alternative approaches.

597

598

599

**Alternative Approach for Comment
Reducing the Reporting Burden Based on Data Collection Timeframe**

600

601 FDA is requesting public comment on possible alternative approaches with regard to data
602 collection timeframes to reduce the burden of data collection. For example, FDA is considering
603 whether to use the manufacturer’s current timeframe for conducting its APRs or PQRs as a
604 possible alternative timeframe for reporting.

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**Alternative Approach for Comment
Including a Limited Text Field for Data Point/Metrics**

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FDA is requesting public comment on possible alternative approaches that would enable a
company to provide an explanation or plan for continual improvement for reported data points or
metrics, while recognizing that FDA may not be able to review each explanation or plan. For
example, FDA is considering whether to include a text field for the submission of 100 word
“free-text” explanations for each data point or metric.

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625 FDA might review explanatory text submitted as an optional metric to clarify any questions
626 raised in the Agency’s analysis of the data. For example, an unexpected decrease in lot
627 acceptance rate may be due to a situation outside the control of the facility (e.g., act of nature
628 like storm or fire). Also, the use of new, in-line analytical technology used for real time release
629 testing with increased sensitivity might result in better detection of in-process OOS results and a
630 temporary increase in total OOS results. However, improved detection that allows for the
631 diversion and rejection of poor quality product will allow for improved assurance of quality. In
632 this instance, it may be appropriate to provide an explanation that new, improved technology was
633 implemented and that there is data demonstrating that more robust product was released to the
634 market as a result of this change (e.g., increased lot uniformity would be appropriate).

635
636 If this approach is adopted, reporting establishments could elect to include an explanation to
637 identify these types of factors. Reporting establishments could also elect to include a continual
638 improvement plan for the next reporting cycle. Note that FDA will likely be unable to review all
639 submitted comments due to the volume of data that will be reported. However, comments might
640 be helpful during evaluation of the data.

641
642 Comments are requested on this or any other possible alternative approaches.

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645 **GLOSSARY**

646
647 **Active Ingredient** (active pharmaceutical ingredient, API)³⁸ – any component that is intended to
648 furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation,
649 treatment, or prevention of disease, or to affect the structure or any function of the body of man
650 or other animals. The term includes those components that may undergo chemical change in the
651 manufacture of the drug product and be present in the drug product in a modified form intended
652 to furnish the specified activity or effect.

653
654 **Annual Product Review** – an evaluation, conducted at least annually, of the quality standards of
655 a drug product to determine the need for changes in drug product specifications or manufacturing
656 or control procedures.³⁹

657
658 **Batch** – a specific quantity of a drug or other material that is intended to have uniform character
659 and quality, within specified limits, and is produced according to a single manufacturing order
660 during the same cycle of manufacture.⁴⁰

661
662 **Corrective Action and Preventive Action (CAPA)**⁴¹

- 663
- 664 • **Corrective Action** – an action to eliminate the cause of a detected nonconformity or other
665 undesirable situation.
 - 666
 - 667 • **Preventive Action** – an action to eliminate the cause of a potential nonconformity or other
668 undesirable potential situation.

669
670 NOTE: Preventive action is taken to prevent occurrence, whereas corrective action is taken to
671 prevent recurrence. (ISO 9000:2005)

672
673 **Critical Quality Attribute (CQA)** – A physical, chemical, biological, or microbiological
674 property or characteristic that should be within an appropriate limit, range, or distribution to
675 ensure the desired product quality.⁴²

676
677 **Establishment** – a place of business under one management at one general physical location.
678 The term includes, among others, independent laboratories that engage in control activities for a
679 registered drug establishment (e.g., contract laboratories).⁴³

680
681 **Invalidated OOS** – any out-of-specification result that was invalidated. Note: Invalidation of a
682 discrete test result may be done only upon the observation and documentation of a test event that

³⁸ See 21 CFR 210.3(b)(7).

³⁹ See 21 CFR 211.180(e).

⁴⁰ See 21 CFR 210.3(b)(2).

⁴¹ Refer to FDA guidance for industry *Q10 Pharmaceutical Quality System*.

⁴² Refer to FDA guidance for industry *Q8(R2) Pharmaceutical Development*.

⁴³ See 21 CFR 207.3(a)(7).

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683 can reasonably be determined to have caused the OOS result.⁴⁴ For the purpose of this guidance,
684 this includes: (1) finished product and stability test results *only* and, (2) all finished product and
685 stability test results that initially appear as OOS, even if invalidated by a subsequent laboratory
686 investigation.

687
688 **Lot** – a batch, or a specific identified portion of a batch, having uniform character and quality
689 within specified limits; or, in the case of a drug product produced by continuous process, it is a
690 specific identified amount produced in a unit of time or quantity in a manner that assures its
691 having uniform character and quality within specified limits.⁴⁵

692
693 **Lot Attempted** – a lot intended for commercial use for which the manufacturer has issued a lot
694 number and charged API (for finished drug manufacturers) or primary starting materials (for API
695 manufacturers).⁴⁶

696
697 **Lot Release Test** – includes all finished product tests, all real time release tests, and all in-
698 process tests that act as a surrogate for finished product lot release.^{47,48}

699
700 **Out-of-Specification (OOS) Result** – all test results that fall outside the specifications or
701 acceptance criteria established in drug applications, drug master file, official compendia, or by
702 the manufacturer.⁴⁹ For the purpose of this guidance, this includes: (1) finished product and
703 stability test results *only* and, (2) all finished product and stability test results that initially appear
704 as OOS, even if invalidated by a subsequent laboratory investigation.

705
706 **Process Capability** – a statistical estimate of the outcome of a characteristic from a process that
707 has been demonstrated to be in a state of statistical control.⁵⁰

708
709 **Process Capability Index** – an index describing process capability in relation to a specified
710 tolerance.⁵¹

711
712 **Process Performance** – a statistical measure of the outcome of a characteristic from a process
713 that may not have been demonstrated to be in a state of statistical control.⁵²

⁴⁴ See 21 CFR 211.160(a) and FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.

⁴⁵ See 21 CFR 210.3(b)(10).

⁴⁶ See 21 CFR 211.101.

⁴⁷ See 21 CFR 211.165.

⁴⁸ This term does not refer to samples and protocols under 21 CFR 610.2.

⁴⁹ See FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.

⁵⁰ See ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.

⁵¹ See ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.

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714
715 **Process Performance Index** – an index describing process performance in relation to specified
716 tolerance.⁵³
717
718 **Product Quality Complaint** – a complaint involving any possible, including actual, failure of a
719 drug product to meet any of its specifications designed to ensure that any drug products conform
720 to appropriate standards of identity strength, quality, and purity.⁵⁴
721
722 **Product Quality Review** – a regular quality review, which should normally be conducted and
723 documented annually, of an API with the objective of verifying the consistency of the process
724 and assessment of whether corrective action or any revalidation should be undertaken.⁵⁵
725
726 **Specification-Related Rejected Lot** – a lot that was rejected because it failed to meet at least
727 one specification.

⁵² See ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.

⁵³ See ASTM E-2281, *Standard Practice for Process and Measurement Capability Indices* (2012), ASTM International, West Conshohocken, PA, DOI: 10.1520/E2281-08AR12E01, www.astm.org. This is not the only useful reference on this topic. Many industry standards, books, and guides on these topics are available.

⁵⁴ See 21 CFR 211.160(b); 211.198.

⁵⁵ The Product Quality Review of APIs is comparable to the Annual Product Review conducted for finished drug products under 21 CFR 211.180(e). Refer to FDA guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*.

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729 **APPENDIX A: INSTRUCTIONS FOR QUALITY METRIC DATA SUBMISSIONS**

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731 FDA intends to include these instructions in the requests for quality metrics data described above
732 in section V. At the time such requests are made, FDA intends to provide additional information
733 about mechanisms for submission.

734

735 **Instructions for Quality Metric Data Submissions – Mandatory Data**

736

737

1. Provide the drug name referenced in the completed data table.

738

739

740

741

- a. Drugs that are subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act and drugs that are covered by a submission to drug master file (DMF) that is intended to support an application – API/drug substance or FDF/drug product name provided in application.

742

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- b. Drugs that are not subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act – API or FDF drug product name. If the drug product name is included as part of registration, the same name included in registration should be used.

746

2. Indicate if the drug referenced in the completed data table is prescription or OTC.

747

748

749

Note: This element is not required to be reported for an API intended for use in the manufacture of a drug product.

750

751

3. Indicate the applicable monograph, if any, for the drug referenced in the completed data table.

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Note: This element is not required to be reported for products that are subject to approved, or covered by a submission to a DMF that is intended to support an application, applications under either section 505 of the FD&C Act or under section 351 of the PHS Act.

757

758

4. Provide the drug type for the completed data table. This is restricted to two options – API or FDF – only one option can be selected.

759

5. Provide the applicant name for the completed data table.

760

761

762

763

- a. Drugs that are subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act and drugs that are covered by a submission to drug master file (DMF) that is intended to support an application – firm name of the application holder.

764

765

- b. Drugs that are not subject to either approved applications under section 505 of the FD&C Act or under section 351 of the PHS Act – N/A.

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- 766 6. Provide the final labeler name for the completed data table.
- 767 a. Drugs that are subject to either approved applications under section 505 of the
768 FD&C Act or under section 351 of the PHS Act and drugs that are covered by a
769 submission to drug master file (DMF) that is intended to support an application–
770 N/A.
- 771 b. Drugs that are not subject to either approved applications under section 505 of the
772 FD&C Act or under section 351 of the PHS Act – firm name of the labeler listed
773 in the NDC code.
- 774 7. Provide the application type for the completed data table.
- 775 a. Drugs that are subject to either approved applications under section 505 of the
776 FD&C Act or under section 351 of the PHS Act and drugs that are covered by a
777 submission to drug master file (DMF) that is intended to support an application–
778 NDA/ANDA/BLA/DMF as applicable.
- 779 b. Drugs that are not subject to either approved applications under section 505 of the
780 FD&C Act or under section 351 of the PHS Act – N/A.
- 781 8. Provide the application number for the drug referenced in the data table.
- 782 a. Drugs that are subject to either approved applications under section 505 of the
783 FD&C Act or under section 351 of the PHS Act and drugs that are covered by a
784 submission to drug master file (DMF) that is intended to support an application–
785 approved NDA/ANDA/BLA/DMF number.
- 786 b. Drugs that are not subject to either approved applications under section 505 of the
787 FD&C Act or under section 351 of the PHS Act – N/A.
- 788 9. Provide the NDC product code for the drug referenced in the data table.
- 789 a. Drugs that are subject to either approved applications under section 505 of the
790 FD&C Act or under section 351 of the PHS Act and drugs that are covered by a
791 submission to drug master file (DMF) that is intended to support an application–
792 N/A.
- 793 b. Drugs that are not subject to either approved applications under section 505 of the
794 FD&C Act or under section 351 of the PHS Act – final labeled NDC product
795 code.
- 796 10. Provide the time period within which the data being reported were collected.
- 797 a. This number should be reported as mm/dd/yyyy – mm/dd/yyyy.

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798 **Refer to the companion technical specification for instructions related to data type, format,**
799 **and range when filling out the remaining information on the data table.**

800
801 11. Provide the number of “lots attempted,” as defined in the glossary, for the drug
802 referenced in (1), segmented by all establishments as described in section V.A and V.D.

803 **Note: If an establishment only performs testing operations, this element is not applicable.**

804 12. Provide the number of “lots rejected,” as defined in the glossary, for the drug referenced
805 in (1), segmented by all establishments as described in section V.A and V.D.

806 **Note: If an establishment only performs testing operations, this element is not applicable.**

807 13. Provide the number of lot release and stability “tests conducted,” for the drug referenced
808 in (1), segmented by all establishments as described in section V.A and V.D. Lot release
809 test is defined in the glossary.

810 **Note: If finished product or stability testing operations are not applicable to the**
811 **operations in which the establishment is engaged, this data point is not applicable.**

812 14. Provide the number of “OOS results,” as defined in the glossary, for the drug referenced
813 in (1), segmented by all establishments as described in section V.A and V.D.

814 **Note: If finished product or stability testing operations are not applicable to the operations**
815 **in which the establishment is engaged, this data point is not applicable.**

816 15. Provide the number of “invalidated OOS” results due to laboratory error, as defined in
817 the glossary, for the drug referenced in (1), segmented by all establishments as described
818 in section V.A and V.D.

819 **Note: If finished product or stability testing operations are not applicable to the operations**
820 **in which the establishment is engaged, this data point is not applicable.**

821 16. Provide the number of “product quality complaints,” as defined in the glossary, for the
822 drug referenced in (1), above, segmented by all establishments as described in section
823 V.A and V.D.

824 **Note: This element should not be segmented by establishment and only one value should**
825 **be reported per quarter. This value should represent all product quality complaints**
826 **received for the drug referenced in (1), above. It can be attributed to the Reporting**
827 **Establishment or one of the other establishments listed in the table. If attributed to**
828 **one of the establishments listed in the table, the Reporting Establishment does not**
829 **need separate rows.**

830 17. Provide the number of “lots released,” as defined in the glossary, for the drug referenced
831 in (1), above, segmented by all establishments as described in section V.A and V.D.

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- 832 18. Provide a “Yes” or “No” for the question “Was the APR (or PQR) generated within 30
833 days of the annual due date?” for drug referenced in (1), above, segmented by all
834 establishments as described in section V.A and V.D. Please refer to the glossary for the
835 definition of APR and PQR.
- 836 19. Provide the DUNS# for each establishment referenced in the application.
- 837 20. Provide the dosage form for the drug that is referenced in (1) – Product Name. The
838 dosage form should be equivalent for all establishments referenced in the application.
- 839 a. **This element is not applicable for establishments that only perform testing**
840 **operations for the product referenced in the data table.**
- 841 21. Provide the FEI # (facility establishment identifier) for each establishment referenced in
842 the application.
- 843 a. **The FEI number should be the same for each quarter (1, 2, 3, and 4) within**
844 **each establishment.**
- 845 22. Select all activity classifications for each establishment referenced in the application.
846 Please restrict the activity chosen for each establishment to the options provided. List the
847 activity name(s) in full (e.g., “Direct Product Manufacturing”).
- 848 a. **The activity classification should be the same for each quarter (1, 2, 3, and 4)**
849 **within each establishment.**

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850 **Worksheet for Data Tables**

851
852 The tables below are worksheets to support the submission of the data in accordance with the instructions above.
853

854 **Product Specific Information**

Product Name	Rx or OTC	Applicable Monograph	Product Type	Applicant	Final Labeler	Application Type	Application Number	NDC Code	Reporting Time Period

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Mandatory Data

Establishment	Quarter (1, 2, 3, or 4)	DUNS #	FEI #	# of Lots Attempted	# of Lots Rejected	# of Tests Conducted	# of OOS Results	# of Invalidated OOS Results	# Product Quality Complaints	# of Lots Released	Was the APR Generated Within 30 Days of Annual Due Date?— Yes or No)	How many APR's or PQR's are associated with the product?	Dosage Form	Activity - Please indicate all that apply - Direct Product Manufacturing, QC Lab ,Other
Reporting Establishment Name	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Reporting Establishment Name	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Reporting Establishment Name	3	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Reporting Establishment Name	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A		N/A	N/A	N/A	N/A	N/A
Establishment 1 Name	1								N/A					
Establishment 1 Name	2								N/A					
Establishment 1 Name	3								N/A					
Establishment 1 Name	4								N/A					
Establishment 2 Name	1								N/A					
Establishment 2 Name	2								N/A					
Establishment 2 Name	3								N/A					
Establishment 2 Name	4								N/A					

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Establishment N Name	n													
								N/A						

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859

Optional Metrics

Establishment	Quarter (1, 2, 3 or 4)	Was each APR or PQR reviewed and approved by the following: (1) the head of the quality unit, (2) the head of the operations unit, (3) both; or (4) neither?	What percentage of your corrective actions involved re-training of personnel (i.e., a root cause of the deviation is lack of adequate training)?	V A “yes” or “no” value of whether the establishment’s management calculated a process capability or performance index for each critical quality attribute (CQA) as part of that product’s APR or PQR.	A “yes” or “no” value of whether the establishment’s management has a policy of requiring a corrective action or preventive action (CAPA) at some lower process capability or performance index.	If “yes” to the above question – what is the process capability or performance index that triggers a CAPA? If “no” to the previous two questions – please do not respond.
Establishment 1 Name	1					
Establishment 1 Name	2					
Establishment 1 Name	3					
Establishment 1 Name	4					

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Establishment 2 Name	1					
Establishment 2 Name	2					
Establishment 2 Name	3					
Establishment 2 Name	4					
Establishment N Name	n					

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