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# Submission of Quality Metrics Data 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## ***DRAFT GUIDANCE***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)**

**November 2016**

Pharmaceutical Quality/CMC  
Current Good Manufacturing Practices (CGMPs)

**Revision 1**

# Submission of Quality Metrics Data Guidance for Industry

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36 majority of voluntary reports will be submitted by establishments engaged in the manufacture,  
37 preparation, propagation, compounding, or processing of finished dosage forms (FDF) of  
38 “covered drug products” or active pharmaceutical ingredients (API) used in the manufacture of  
39 “covered drug products.”<sup>5</sup>

40  
41 The voluntary reporting phase of the program described in this guidance is not focused on  
42 reporting from certain CDER regulated manufacturers (i.e., compounders operating under  
43 section 503A or registered as outsourcing facilities under section 503B of the Federal Food,  
44 Drug, and Cosmetic Act (FD&C Act) or CBER regulated manufacturers of blood and blood  
45 components for transfusion, vaccines, in vitro diagnostics,<sup>6</sup> cell therapy products, gene therapy  
46 products, allergenic extracts, human cells, tissues, and cellular and tissue based products).<sup>7</sup>

47  
48 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
49 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
50 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
51 the word *should* in Agency guidances means that something is suggested or recommended, but  
52 not required. Also, in this guidance, the use of the word *should* is used to indicate an FDA  
53 preference to promote consistent reporting and counting of quality metrics data.<sup>8</sup>

54  
55

56 **II. BACKGROUND**

57

58 **A. Modernization of Regulatory Oversight of Drug Quality and Promotion of**  
59 **Post-Approval Improvements**

60

61 FDA’s approach to quality oversight has evolved in recent years. CDER and CBER are  
62 committed to supporting the modernization of pharmaceutical manufacturing as part of the  
63 Agency’s mission to protect and promote public health. This effort is also part of a long-term  
64 strategy to mitigate drug shortages by addressing the underlying causes of shortages, as noted in  
65 *FDA’s Strategic Plan for Preventing and Mitigating Drug Shortages*.<sup>9</sup> In 2002, FDA launched  
66 an initiative entitled “Pharmaceutical cGMPs for the 21<sup>st</sup> Century: A Risk-Based Approach,” to  
67 encourage the implementation of a modern, risk-based pharmaceutical quality assessment

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<sup>5</sup> The terms “covered drug product” and “covered establishment” are defined in section III.A.

<sup>6</sup> This guidance is not applicable to biological products that meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

<sup>7</sup> The guidance does apply to licensed biological products that are plasma derived products, including recombinant and transgenic versions of plasma derivatives.

<sup>8</sup> FDA intends to accept voluntary reports with quality metrics data that are inconsistent with the metrics and definitions in this guidance, as well as reports about establishments and products that are not the focus of the voluntary reporting phase of the quality metrics program as described in this guidance. However, as the data submitted in a manner inconsistent with the definitions and recommendations in this guidance may not be comparable with submissions from other reporters, we: (1) do not intend to include these reporters on the quality metrics reporters list, and (2) may not be able to integrate the submission of the report into FDA’s risk-based inspection model. Submissions will be evaluated on a case-by-case basis.

<sup>9</sup> See *FDA’s Strategic Plan for Preventing and Mitigating Drug Shortages* at: <http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf>.

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68 system.<sup>10</sup> The initiative was published with several goals, including ensuring that regulatory  
69 review, compliance, and inspection policies support continuous improvement and innovation in  
70 the pharmaceutical manufacturing industry. Since publication of the Pharmaceutical cGMPs for  
71 the 21<sup>st</sup> Century, CDER has promoted a vision of “a maximally efficient, agile, flexible  
72 manufacturing sector that reliably produces high-quality drug products without extensive  
73 regulatory oversight.”<sup>11</sup>

74  
75 FDA encourages manufacturers to routinely use additional quality metrics beyond the metrics  
76 described in this guidance in performing product and establishment specific evaluations.<sup>12</sup> The  
77 selected metrics are not intended to be an all-inclusive set of the quality metrics that  
78 manufacturers may find useful to assess a product and manufacturer’s state of quality.

79  
80 **B. Quality Metrics Data – Regulatory Foundation**

81  
82 FDA understands that establishments involved in the manufacture, preparation, propagation, or  
83 processing of human drugs, including oversight to ensure quality,<sup>13</sup> currently use quality metrics  
84 as part of the process validation lifecycle and pharmaceutical quality system (PQS) assessment.<sup>14</sup>  
85 The metrics described in this guidance could be a part of such oversight.

86  
87 As described in FDA’s process validation guidance, manufacturers depend on information and  
88 knowledge from product and process development as the basis for establishing an approach to  
89 control of the manufacturing process (i.e., a control strategy) that results in products with the

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<sup>10</sup> See *Pharmaceutical cGMP’s for the 21<sup>st</sup> Century: A Risk-Based Approach* at:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/ucm137175.htm>.

<sup>11</sup> See *FDA Pharmaceutical Quality Oversight: One Quality Voice* at  
<http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM442666.pdf>.

<sup>12</sup> One type of evaluation is an internal, independent audit and review of processes and procedures to determine whether established protocols and procedures have been followed. FDA’s Compliance Policy Guide Sec. 130.300, FDA Access to Results of Quality Assurance Program Audits and Inspections (June 2, 2007) describes our policy that during routine inspections and investigations, FDA will not review or copy these specific reports and records to encourage firms to conduct candid and meaningful audits and inspections. The voluntary submission of quality metrics data described in this guidance will be for specific data that are maintained on-site, routinely reviewed during inspections, and not subject to a request for the results of an internal audit.  
<http://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm073841.htm>.

<sup>13</sup> Food and Drug Administration Safety and Innovation Act of 2012 (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.

<sup>14</sup> Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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90 desired quality attributes.<sup>15</sup> Once a control strategy has been successfully implemented,  
91 manufacturers are expected to maintain the process in a state of control over the life of the  
92 process, even as materials, equipment, production environment, personnel, and manufacturing  
93 procedures change.<sup>16</sup> Current good manufacturing practice (CGMP) for human drugs require  
94 manufacturers to have an ongoing program to maintain and evaluate product and process data  
95 that relate to product quality.<sup>17</sup> Best practice for this ongoing assessment is continued process  
96 verification,<sup>18</sup> which should include a Periodic Product Review (PPR), conducted at least  
97 annually, in which data collected includes relevant process trends and quality of incoming  
98 materials or components, in-process materials, and finished products. Some establishments may  
99 call this evaluation an Annual Product Review (if conducted annually) or a Product Quality  
100 Review,<sup>19</sup> for finished drug products or APIs, respectively. We expect that most of the quality  
101 metrics data described in this guidance will be collected by establishments already as part of  
102 conducting the PPR.

103  
104 Under Title VII section 706 of the Food and Drug Administration Safety and Innovation Act  
105 (FDASIA) Public Law No. 112-144, FDA may require the submission of any records or other  
106 information that FDA may inspect under section 704 of the FD&C Act, in advance or in lieu of  
107 an inspection by requesting the records or information from a person that owns or operates an  
108 establishment that is engaged in the manufacture, preparation, propagation, compounding, or  
109 processing of a drug. The quality metrics data described in this guidance is information of the  
110 type that FDA may inspect under section 704 of the FD&C Act. However, FDA does not intend  
111 to require the submission of information pursuant to section 704(a)(4) of the FD&C Act in  
112 implementing the voluntary phase of the quality metrics reporting program. FDA does not  
113 intend to take enforcement action based on errors in a quality metrics data submission made as a  
114 part of this voluntary phase of the reporting program, provided the submission is made in good  
115 faith.

116  
117 Section 510(h)(3) of the FD&C Act requires a risk-based inspection schedule for drug  
118 establishments according to the known safety risks posed by establishments that are required to  
119 register. These risks are based on certain factors described in section 510(h)(4)(A-F), including  
120 the inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at  
121 the establishment and other factors. FDA intends to analyze the calculated quality metrics to  
122 support its understanding of the safety risks of manufacturing establishments and products, and  
123 as the basis for criteria it deems necessary and appropriate for allocating inspection resources.

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<sup>15</sup> 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.

<sup>16</sup> 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 and establishing the safety of raw materials, materials used in the manufacturing of drugs, and finished drug products.

<sup>17</sup> See 21 CFR 211.180(e) and section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)).

<sup>18</sup> Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1).

<sup>19</sup> 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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**III. REPORTING OF QUALITY DATA AND CALCULATION OF QUALITY METRICS**

**A. Who Reports and Who May Contribute to a Report**

*1. Covered Establishments and Covered Drug Products*

Except as noted below, owners and operators of each establishment that is engaged in the manufacture, preparation, propagation, compounding, or processing of a covered drug product, or an API used in the manufacture of a covered drug product, may submit quality metrics data. For purposes of this guidance, we will refer to the types of establishments whose owners or operators directly or indirectly submit reports as “covered establishments.”

For purposes of reporting a covered drug product or an API used in the manufacture of a covered drug product, a covered drug product is:

- subject to an approved application under section 505 of the FD&C Act or under section 351 of the Public Health Service Act (PHS) Act,
- marketed pursuant to an OTC monograph, or
- a marketed unapproved finished drug product.

Covered establishments also include (but are not limited to) contract laboratories, contract sterilizers, contract packagers,<sup>20</sup> and other establishments, as appropriate, engaged in the manufacture, preparation, propagation, compounding, or processing of a covered drug product or API used in a covered drug product.

*2. Who Reports for Covered Establishments*

This guidance describes two types of quality metric data reports: (1) product reports submitted by product reporting establishments,<sup>21</sup> and (2) site reports submitted by site reporting establishments. We encourage reports from product reporting establishments and site reporting establishments. FDA prefers for all covered establishments to work with a product reporting establishment and report data for the covered drug product so that the product reporting establishment submits a single product report that includes data from all covered establishments.

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<sup>20</sup> Contract re-packagers that purchase product and repackage it into a different *primary packaging* configuration are included (e.g., large bottles of tablets repackaged into unit dose blister packs). Contract re-packagers that purchase product and repackage into secondary or tertiary packaging are not included.

<sup>21</sup> A “product reporting establishment” is one establishment who will already possess or have access to all of the quality metrics data needed to submit such reports. It is further defined in section III.A.2.a.



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162 Compilation of data into a single product report will facilitate data analysis and identification of  
163 product specific issues (e.g., potential loss in drug supply).  
164

165 a. Submission of a product report by a product reporting establishment  
166

167 The subject of a product report will generally be a covered drug product or an API used in the  
168 manufacture of a covered drug product. The report may include quality metrics data from each  
169 covered establishment within the manufacturing supply chain that has the data described in this  
170 guidance. FDA believes that, as part of its responsibility for oversight and controls over the  
171 manufacture of drugs to ensure quality, one establishment will already possess or have access to  
172 all of the quality metrics data needed to submit such reports — for example, through contract or  
173 because all of the covered establishments with quality metrics data related to a covered drug  
174 product or API used in the manufacture of a covered drug product will be under common  
175 ownership or control.<sup>22</sup> This establishment should combine the data so that a single report is  
176 submitted. For example, a single API may be the subject of a stand-alone product report, as  
177 APIs are often supplied to multiple customers and finished drug product manufacturers often use  
178 multiple API suppliers.  
179

180 In this guidance, we refer to the covered establishments that submit product reports to FDA as  
181 “product reporting establishments.” If a product reporting establishment is gathering data from  
182 covered establishments in the manufacturing supply chain for a particular product for the  
183 purpose of submitting a product report, but data is not available for a covered establishment,  
184 FDA prefers that the product report clearly identifies the covered establishment and that specific  
185 data was not received.<sup>23</sup>  
186

187 FDA believes that the quality control unit (QCU)<sup>24</sup> in each reporting establishment for a covered  
188 drug product or API used in a covered drug product will generally be best positioned to compile  
189 reports for submission to FDA, considering the QCU responsibilities and authorities for the  
190 oversight of drugs as described in 21 CFR 211.22.<sup>25</sup>  
191

192 b. Submission of a site report by a site reporting establishment  
193

194 If the covered establishment prefers to report directly or is unsure if all products and data will be  
195 reported via a product report, the covered establishment may elect to submit a site report. In this  
196 guidance, we refer to the covered establishments that submit site reports to FDA as “site  
197 reporting establishments.”  
198

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<sup>22</sup> See, e.g., FDASIA section 711; 21 CFR 200.10(b).

<sup>23</sup> Refer to Appendix A.1, A.2, A.3, and A.4.

<sup>24</sup> For the purpose of this guidance, the term “quality control unit” is synonymous with “quality unit.”

<sup>25</sup> For APIs, these responsibilities are described in FDA guidance for industry *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (section 2.2).

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199 The subject of a site report is a single covered establishment. A complete report would list all  
200 covered products with associated quality metric data specific to each product manufactured at the  
201 subject establishment as described in this guidance.<sup>26</sup>

202  
203 **B. Quality Metrics that FDA Intends to Calculate**

204  
205 The following set of quality metrics that FDA intends to calculate based on industry reporting  
206 was developed with stakeholder input. FDA used the following selection criteria in developing  
207 the set of data that it is inviting covered establishments to submit: (1) objective data to provide  
208 consistency in reporting, (2) of the type contained in records subject to inspection under section  
209 704 of the FD&C Act, and (3) a valuable component in assessing the overall effectiveness of a  
210 PQS, within reasonable limits, and in a reasonable manner, while avoiding an undue reporting  
211 burden. FDA believes that these quality metrics data, in conjunction with other data accessible  
212 to FDA, provide important information about operational reliability.

213  
214 Using reported data described in the following section, FDA intends to calculate quality metrics  
215 for each product and covered establishment, where applicable:

- 216  
217 • **Lot Acceptance Rate (LAR)** as an indicator of manufacturing process performance.  
218 LAR = the number of accepted lots in a timeframe divided by the number of lots started  
219 by the same covered establishment in the current reporting timeframe.  
220
- 221 • **Product Quality Complaint Rate (PQCR)** as an indicator of patient or customer  
222 feedback. PQCR = the number of product quality complaints received for the product  
223 divided by the total number of dosage units distributed in the current reporting timeframe.  
224
- 225 • **Invalidated Out-of-Specification (OOS) Rate (IOOSR)** as an indicator of the operation  
226 of a laboratory. IOOSR = the number of OOS test results for lot release<sup>27</sup> and long-term  
227 stability testing invalidated by the covered establishment due to an aberration of the  
228 measurement process divided by the total number of lot release and long-term stability  
229 OOS test results in the current reporting timeframe.<sup>28,29</sup>

230  
231 **C. Quality Metrics Data that May Be Reported**

232  
233 Section IV.B describes the types of metrics FDA intends to calculate and the associated data that  
234 may be submitted to calculate and understand each metric. FDA encourages product reporting  
235 establishments to submit product reports, segmented by covered establishment, where possible.<sup>30</sup>

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<sup>26</sup> Refer to Appendix A.5, A.6, A.7, and A.8.

<sup>27</sup> This term does not refer to samples and protocols under 21 CFR 610.2.

<sup>28</sup> Reference this guidance's Glossary for OOS result (e.g., lot release tests and long-term stability tests only). A single result (e.g., one value on a Certificate of Analysis) may result in only one OOS test result.

<sup>29</sup> The metric measures invalidated lot release OOS results and long-term stability OOS results, separately.

<sup>30</sup> FDA anticipates that data relevant to contract laboratories will generally be limited to the number of OOS results, the number of lot release and stability tests conducted, and the number of invalidated OOS.

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236 The quality metrics data described in this draft guidance is developed and maintained in the  
237 course of manufacturing drugs in compliance with CGMP. In general, the information that FDA  
238 will receive is maintained in accordance with 21 CFR 211 subpart J and evaluated under 21 CFR  
239 211.180(e). For non-finished drug products (e.g., APIs), refer to section 501(a)(2)(B) of the  
240 FD&C Act and FDA guidance for industry *Q7 Good Manufacturing Practice Guidance for*  
241 *Active Pharmaceutical Ingredients*. Data that is summed and reported as described in this  
242 section is in a readily accessible format for analysis.

243  
244 Reporting of data related to lots of drugs that are imported, intended for import into the United  
245 States, or manufactured in the United States is preferred. However, FDA recognizes that it may  
246 not be possible for some covered establishments to identify started lots, rejected lots, and OOS  
247 results that are specific to drugs that are imported, intended for import, or manufactured in the  
248 United States. Further, lots manufactured outside of the United States may be split after  
249 manufacturing is completed and a portion is imported, or intended for import into the United  
250 States. In these instances, if the manufacturing process uses the same process and controls data  
251 for lots that are not specific to those that are imported, intended for import, or manufactured in  
252 the United States, the report could include both data from lots *not* imported or intended for  
253 import to the United States with the data from lots imported or intended for import to the United  
254 States for the lot acceptance and invalidated OOS metrics. The selection of drugs that are either:  
255 (1) imported, intended for import, or manufactured in the United States, or (2) all drugs using the  
256 same manufacturing process and controls which are not necessarily imported, intended for  
257 import, or manufactured in the United States, should remain consistent within and across  
258 reporting cycles, unless otherwise specified. Product quality complaint data should be related to  
259 drugs that are imported, intended for import or manufactured in the United States.

260  
261 Reporting of data should include all manufacturing operations, including testing, which would be  
262 included in a PPR (e.g., lots intended for commercial distribution, post-approval clinical trial lots  
263 when the same manufacturing process and controls are used as for commercial lots).

264  
265 (1) Lot Acceptance Rate (LAR) Data:

- 266
- 267 • The number of saleable lots *started* which are intended for primary packaging or  
268 distribution.
  - 269
  - 270 • The number of saleable lots *released* for primary packaging or distribution.
  - 271
  - 272 • The number of saleable lots started which are intended for primary packaging or  
273 distribution and were *rejected*.
  - 274
  - 275 • The number of lots *started* of in-process and packaging product lots which are intended  
276 for distributed product.
  - 277
  - 278 • The number of in-process and packaging product lots *released* which are intended for  
279 distributed product.
- 280

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- 281       • The number of in-process and packaging product lots which were intended for distributed  
282       product and were *rejected*.

283  
284   Specific criteria for the LAR data:

- 285
- 286       • Examples of saleable lots include bulk tablets, filled vials, bulk milled in-process material  
287       if manufacturing is performed at another covered establishment, bulk API, and bulk  
288       intermediate API if further manufacturing is performed at another covered establishment.  
289
  - 290       • A lot may be subdivided or grouped after the first started lot is initiated. Each subsequent  
291       subdivision or grouping is considered a separate lot.  
292
  - 293       • Examples of packaging product lots include multiple packaging configurations of bulk  
294       tablets (e.g., small bottles, large bottles, blisters) and labeling filled sterile vials with  
295       multiple labels (e.g., intended for different countries). The packaging operation can be  
296       stand-alone lots or included in an existing lot.  
297
  - 298       • In general, FDA anticipates that the number of lots *started* minus the sum of lots *released*  
299       and lots *rejected* will equal the total number of lots pending disposition (e.g., work in  
300       progress, lots evaluated for batch release, lots pending disposition due to quality-related  
301       discrepancies). We recognize that there are rare instances when this construct will not be  
302       valid (e.g., lots pending disposition for an extended period) and we encourage the use of  
303       the comment text box to explain the occurrence of such an anomaly.  
304

305   (2) Invalidated OOS Rate Data (IOOSR):

- 306
- 307       • The number of lot release test OOS and long-term stability OOS results for the finished  
308       drug product or API where the long-term stability test supports the labeled expiration  
309       date.  
310
  - 311       • The total number of lot release and long-term stability tests conducted for the finished  
312       drug product or API where the long-term stability test supports the labeled expiration  
313       date.  
314
  - 315       • The number of OOS results for lot release tests and long-term stability tests for the  
316       finished drug product or API where the source of the OOS result is identified as an  
317       aberration of the measurement process and where the stability test supports the labeled  
318       expiration date.  
319

320   Specific criteria for the IOOSR data:

321

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- 322 • An investigation must be conducted whenever an OOS result is obtained.<sup>31</sup> For the  
323 purpose of the quality metrics program, the following OOS results should be counted:  
324 (1) finished drug product and API and long-term stability test results only, and (2) all  
325 finished drug product and API and long-term stability test results that initially indicate  
326 OOS, even if the source of the OOS is investigated and determined to be an aberration of  
327 the measurement process. See FDA guidance for Industry *Investigating Out-of-*  
328 *Specification (OOS) Test Results for Pharmaceutical Production (October 2006)*, section  
329 III, and FDA guidance for industry *Sterile Drugs Products Produced by Aseptic*  
330 *Processing – Current Good Manufacturing Practice (September 2004)*, section XI.  
331
- 332 • The number of total tests is a measurement tool that: (1) provides context for the  
333 invalidated OOS rate, and (2) provides a secondary metric for manufacturing  
334 performance and the ability to produce product within limits (lot release and long-term  
335 stability OOS results investigated as a manufacturing aberration divided by the total  
336 number of lot release and long-term stability tests performed in the same current  
337 reporting period).  
338
- 339 • For the purpose of this program, an OOS result should be counted on the day that the test  
340 result is completed or the day that an OOS investigation is initiated.  
341
- 342 • A test includes a single analytical result for lot release or a stability timepoint with an  
343 established limit (e.g., analytical chemistry, release sterility test). For example: (1) for  
344 lot release, the final content uniformity result as reported on a Certificate of Analysis is  
345 considered one test; (2) for a stability timepoint, each test performed in the timepoint  
346 would count as an individual test.  
347
- 348 • A covered establishment that manufactures API used in a covered drug product is not  
349 expected to report stability OOS results.  
350
- 351 • For stability testing, only tests that support real-time stability of the product should be  
352 counted (i.e., accelerated stability testing is excluded).  
353
- 354 • If a lot release or long-term stability test is conducted multiple times for a lot (e.g., a  
355 retest), each test should be counted.  
356
- 357 • FDA recognizes the importance of other types of testing not discussed in this guidance  
358 (e.g., in-process testing, environmental testing, raw material and packaging component  
359 testing). However, results of these tests should not be counted in this report.  
360

361 (3) Product Quality Complaint Rate (PQCR):  
362

- 363 • The number of product quality complaints received for the product.

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<sup>31</sup> See 21 CFR 211.192 and section 501(a)(2)(B) of the FD&C Act.

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- The total number of dosage units distributed for the product.

Specific criteria for the PQCR data:

- The total number of all product quality complaints is based on the definition in the glossary. This number does not include multiple counting of the same product quality complaint if the complaint receiver forwards the complaint to individual manufacturers for further investigation. This number does include all potential quality issues, such as subpotency (e.g., a patient report of lack of effect).
- The total number of dosage units distributed for the product is defined in the glossary.

**D. How to Submit Comments Within a Quality Metric Data Report and How to Pose Questions to FDA**

Reporting establishments may submit a 300-word text comment to provide an explanation of submitted data or report plans for improvement. FDA may refer to the comments if unusual data or trends are identified, or in preparation for an on-site inspection. The submission of comments is optional. In the future, FDA may consider establishing a set of codes to standardize the comments.

Comments may describe special situations, such as natural disasters, the use of emerging technology, or describe the manufacturing supply chain or a plan for improvement. For example, an unexpected decrease in lot acceptance rate may be due to a situation outside the control of the facility (e.g., an act of nature such as a storm or fire). For emerging technology, the use of new, in-line analytical technology used for real time release testing with increased sensitivity might result in better detection of in-process OOS results used for Real Time Release Testing and thus, a temporary increase in total OOS results. However, improved detection that allows for the diversion and rejection of poor quality product will provide improved assurance of quality. In this instance, it may be appropriate to provide an explanation that new, improved technology was implemented and that there is data demonstrating that more robust product was released to the market as a result of this change (e.g., increased lot uniformity would be appropriate).

Upon gathering this data, any questions that a covered establishment may have about their specific situation can be sent to [OPQ-OS-QualityMetrics@fda.hhs.gov](mailto:OPQ-OS-QualityMetrics@fda.hhs.gov).

**E. How to Report Quality Metrics Data to FDA**

To facilitate the quality metrics reporters list as described in section IV.B, a defined reporting period (e.g., a single calendar year) is needed to reduce discrepancies between site and product reporting. Therefore, reporting establishments may submit quality metrics data reports where the

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407 data is segmented on a quarterly basis throughout a single calendar year.<sup>32</sup> FDA expects to begin  
408 the data analysis when the portal is closed and then publish initial findings and the quality metric  
409 reporters list on the FDA Web site.

410  
411 Appendix A of the draft guidance is a quality component list with the information for submission  
412 into the electronic portal as well as a description of applicable quality metrics data elements  
413 relevant for different business segments/types. The associated Technical Conformance Guide  
414 describes additional technical details.<sup>33</sup>

415  
416

417 **IV. THE USE OF QUALITY METRICS AND PUBLIC REPORTING**

418  
419 **A. How FDA Intends to Use Quality Metrics**

420  
421 FDA intends to use data from the quality metrics reporting program to focus the use of FDA  
422 resources on the areas of highest risk to public health (e.g., risk-based inspection scheduling).  
423 Specifically, we intend to:

- 424
- 425 • establish a signal detection program as one factor in identifying establishments and
  - 426 products that may pose significant risk to consumers;
  - 427 • identify situations in which there may be a risk for drug supply disruption;
  - 428 • improve the effectiveness of establishment inspections; and
  - 429 • improve FDA’s evaluation of drug manufacturing and control operations.

430  
431 Shortages of drugs can pose a significant public health threat; delaying, and in some cases even  
432 denying, critically needed care for patients. Taking action to reduce drug shortages remains a  
433 top priority for FDA. The Agency has found that the majority of drug shortages stem from  
434 quality concerns—substandard manufacturing facilities or processes are discovered, or  
435 significant quality defects are identified in finished drug product, necessitating remediation  
436 efforts to fix the issue, which in turn, may interrupt production and cause a drug shortage. FDA  
437 intends to use quality metrics, along with other measures, to identify potential shortage signals  
438 and engage proactively with manufacturers to mitigate the likelihood of occurrence.

439  
440 FDA may not be able to accomplish the overall goals of an FDA quality metrics reporting  
441 program, as described in this draft guidance, from voluntary reporting alone. If FDA does not  
442 receive a large body of data from reporting establishments, the ways in which the Agency can  
443 use the information may be limited. For example, data received may not constitute a  
444 representative sample of the industry. Further, a self-selection bias may increase the risk of  
445 signaling an outlier where none exists. For these reasons, we expect to use the information  
446 collected to specifically focus on: (1) working with establishments towards early resolution of

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<sup>32</sup> More details about the timing of the program are in the notice announcing the availability of this draft guidance in the *Federal Register*.

<sup>33</sup> See <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM508464.pdf>.

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447 potential quality problems and to reduce the likelihood that the establishment’s operations will  
448 be disrupted and impact the drug supply, (2) helping to prepare for and direct our inspections,  
449 and (3) using the calculated metrics as an element of the post-approval manufacturing change  
450 reporting program with an emphasis on encouraging lifecycle manufacturing improvement.

451  
452 While FDA recognizes the value of quality metrics, we also recognize that the individual data  
453 points and metrics described in this guidance, either individually or in combination, do not  
454 definitively quantitate the quality of the establishment or its products. Further, FDA continues to  
455 encourage the adoption of emerging technology. We request comments on implementing new  
456 technology while maintaining robust quality metrics programs.

457  
458 FDA intends to publish an analysis of the quality metrics data received on the FDA Web site to  
459 share what the Agency has learned from the voluntary phase of the reporting program, and how  
460 analyzing these data has affected the frequency of CGMP inspections and the ability of the  
461 Agency to address potential drug shortage situations. We also intend to provide opportunities for  
462 participating establishments to provide feedback and additional comments, as well as share  
463 knowledge from ongoing, industry-driven quality metrics programs.

464  
465 **B. Quality Metric Reporters List**

466  
467 FDA intends to publish a list of the names of establishments that voluntarily report all or a subset  
468 of quality data as described in this guidance (i.e., product reporting establishments and site  
469 reporting establishments). We believe that there is a benefit to publicly sharing the names of  
470 establishments that voluntarily choose to submit these quality data to FDA because, through their  
471 participation, these establishments demonstrate a willingness to proactively engage with the  
472 Agency in pursuit of the goals described in this guidance. Participation in this voluntary  
473 reporting phase of the program also demonstrates a commitment to increasing transparency  
474 between industry and FDA and a contribution to improving quality monitoring throughout the  
475 industry.

476  
477 This list may be useful to establishments within the pharmaceutical manufacturing industry when  
478 selecting contract manufacturers and component suppliers as one element of robust outsourcer or  
479 supplier selection (e.g., past inspection and regulatory authority history, audits of the facility and  
480 associated systems, and analytical testing). This list may also be useful for healthcare purchasing  
481 organizations, healthcare providers, patients, and consumers in sourcing drugs when used in  
482 conjunction with other information (e.g., inspection history). The list will provide information  
483 about *whether* an establishment voluntarily submitted quality metrics data to the Agency, and if  
484 so how much data was submitted. It should be noted that inclusion on the list is not an indication  
485 of FDA’s *evaluation* of the submitted data.

486  
487 The Agency will identify participating establishments on FDA’s Web Site according to the  
488 following recognition categories:

- 489
- 490 • For Product Reporting Establishments (finished drug product reporter or API reporter):
- 491



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- 492           ○ Product Reporter Top Tier: If complete data supporting all metrics were  
493           included for each covered establishment in the manufacturing supply chain for  
494           all covered drug products (or APIs used in the manufacture of a covered drug  
495           product) for the full year reporting period  
496
- 497           ○ Product Reporter Mid Tier: If all covered establishments in the manufacturing  
498           supply chain for all covered products were identified in the report, and complete  
499           quality metric data was provided from at least one of the establishments for each  
500           covered drug products (or APIs used in the manufacture of a covered drug  
501           product) for the full year reporting period  
502
- 503           ○ Product Supply Chain Reporter:<sup>34</sup> If all covered establishments in the  
504           manufacturing supply chain for all covered drug products (or APIs used in the  
505           manufacture of a covered drug product) were identified in the report  
506
- 507           ● For Site Reporting Establishments (finished drug product reporter or API reporter):<sup>35</sup>  
508
- 509           ○ Site Reporter Top Tier: If complete data supporting all metrics were included  
510           for all covered drug products (or APIs used in the manufacture of a covered drug  
511           product) for the full year reporting period  
512
- 513           ○ Site Reporter Mid Tier: If complete data supporting all metrics were included  
514           for at least one covered drug product (or API used in the manufacture of a  
515           covered drug product) manufactured at an establishment for the full year  
516           reporting period  
517

518 For example, if product reporting establishment Company ABC submitted a report identifying all  
519 covered establishments in the manufacturing supply chain for all covered drug products (or APIs  
520 used in the manufacture of a covered drug product), but did not provide quality metrics data,  
521 Company ABC would have a “Product Supply Chain Reporter” designation. If product reporting  
522 establishment Company ABC submitted a report identifying all establishments in the  
523 manufacturing supply chain for all covered drug products (or APIs used in the manufacture of a  
524 covered drug product), and metrics data was provided from the primary manufacturing  
525 establishment for each product or API, but incomplete data was submitted from the other  
526 establishments in the manufacturing supply chain, Company ABC would have a “Product  
527 Reporter Mid Tier” designation. If product reporting establishment Company ABC submitted a  
528 complete report for the data listed above for all covered drug products (or APIs used in the  
529 manufacture of a covered drug product), Company ABC would have a “Product Reporter Top  
530 Tier” designation.

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<sup>34</sup> “Product Supply Chain Reporter” is defined for the purpose of FDA’s quality metric reporting program and is not associated with Title II of the Drug Quality and Security Act, the Drug Supply Chain Security Act (DSCSA).

<sup>35</sup> An establishment may be considered a site reporting establishment by either: (1) directly submitting data to FDA (not applicable for product reporting establishments), or (2) indirectly submitting data to FDA via a product report, submitted by a product reporting establishment.

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531  
532 For site reporters, if contract manufacturer Company XYZ manufactures 30 covered drug  
533 products and submitted a report with at least one covered drug product produced at the  
534 establishment and data supporting all metrics, Company XYZ would have a “Site Reporter Mid  
535 Tier” designation. If the report contains data for all 30 products and all metrics for each covered  
536 drug product, Company XYZ would have a “Site Reporter Top Tier” designation. Alternatively,  
537 if Company XYZ submitted data to reporting establishments and the data covers each product  
538 manufactured at the site, and the submitted product reports reference this establishment,  
539 Company XYZ would also have a “Site Reporter Top Tier” designation.

540  
541 FDA does not intend to publicly disclose information submitted to the Agency as part of the  
542 voluntary phase of the quality metrics program that is exempt from disclosure under the Freedom  
543 of Information Act as confidential commercial information, e.g., information that would reveal  
544 nonpublic commercial relationships and production volumes.

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545 **GLOSSARY**

546  
547 **Active Pharmaceutical Ingredient (API)**<sup>36</sup> – any substance that is intended for incorporation  
548 into a finished drug product and is intended to furnish pharmacological activity or other direct  
549 effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the  
550 structure or any function of the body. Active pharmaceutical ingredient does not include  
551 intermediates used in the synthesis of the substance. The term includes those components that  
552 may undergo chemical change in the manufacture of the drug product and be present in the drug  
553 product in a modified form intended to furnish the specified activity or effect.

554  
555 **Batch** – a specific quantity of a drug or other material that is intended to have uniform character  
556 and quality, within specified limits, and is produced according to a single manufacturing order  
557 during the same cycle of manufacture.<sup>37</sup> A batch may be comprised of one lot or multiple lots.

558  
559 **Continued Process Verification** – A process validation activity where ongoing assurance is  
560 gained during routine production that the process remains in a state of control.<sup>38</sup>

561  
562 **Critical Quality Attribute (CQA)** – A physical, chemical, biological, or microbiological  
563 property or characteristic that should be within an appropriate limit, range, or distribution to  
564 ensure the desired product quality.<sup>39</sup>

565  
566 **Dosage Units** – the total number of individual dosage units (e.g., 100,000 tablets, 50,000 vials,  
567 50 kg), distributed or shipped under the approved application or product family (for non-  
568 application products) to customers, including distributors.<sup>40</sup>

569  
570 **Establishment** – a place of business under one management at one general physical location.  
571 The term includes, among others, independent laboratories that engage in control activities for a  
572 registered drug establishment (e.g., consulting laboratories).<sup>41</sup>

573  
574 **Finished Dosage Form (FDF)** – the physical manifestation of a drug product that contains the  
575 active ingredient(s) and/or inactive ingredients that are intended to be delivered to the patient.  
576 Examples include tablets, capsules, vials, solutions, creams, or ointments.<sup>42</sup>

577  
578 **Finished Drug Product** – a finished dosage form (FDF) (e.g., tablet, capsule, or solution) that  
579 contains at least one active pharmaceutical ingredient, generally, but not necessarily, in  
580 association with other ingredients in finished package form suitable for distribution to

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<sup>36</sup> Refer to 21 CFR 207.1 (effective November 29, 2016) and 21 CFR 210.3(b)(7).

<sup>37</sup> See 21 CFR 210.3(b)(2).

<sup>38</sup> Refer to FDA guidance for industry *Process Validation: General Principles and Practices* (Rev 1).

<sup>39</sup> Refer to FDA guidance for industry *Q8(R2) Pharmaceutical Development*.

<sup>40</sup> See 21 CFR 314.81(b)(2)(ii)(a), 211.196.

<sup>41</sup> See 21 CFR 207.1 (effective November 29, 2016).

<sup>42</sup> Refer to “dose form” as defined in ISO 11616:2012(en), *Health informatics – Identification of medicinal products – Data elements and structures for the unique identification and exchange of regulated pharmaceutical product information*.

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581 pharmacies, hospitals, or other sellers or dispensers of the drug product to patients or  
582 consumers.<sup>43</sup>

583  
584 **Long-term testing** – Stability studies under the recommended storage condition for the retest  
585 period or shelf life proposed (or approved) for labeling.<sup>44</sup>

586  
587 **Lot** – a batch, or a specific identified portion of a batch, having uniform character and quality  
588 within specified limits; or, in the case of a drug product produced by continuous process, it is a  
589 specific identified amount produced in a unit of time or quantity in a manner that assures its  
590 having uniform character and quality within specified limits.<sup>45</sup>

591  
592 **Accepted Lot** – a started lot which has been released for distribution or for the next stage  
593 of processing. If the lot is released with an unexpectedly low yield due to an assignable  
594 root cause and the associated investigation supports the release of the lot, it should be  
595 considered an accepted lot.<sup>46</sup> Investigations into low yield results should be thorough and  
596 managed by the quality unit. If a lot number is closed, the lot is transferred to a new lot  
597 number, and subsequently released, only the original lot should be counted. An accepted  
598 lot should be counted on the day of the final disposition decision. It may be possible that  
599 an accepted lot is no longer considered accepted (e.g., a stability failure, a quality  
600 problem identified by a contract packager, or in the marketplace). In this case, the lot  
601 should no longer be counted as an accepted lot. If the change in disposition decision is  
602 after submission of quality data, the reporter may submit an amendment and it would be  
603 helpful if the amendment is available for discussion during a future on-site inspection.

604  
605 **Started Lot** – a lot intended for commercial use for which the manufacturer has issued a  
606 lot number, physically charged API (for finished drug manufacturers) or primary starting  
607 materials (for API manufacturers), and there will be a disposition decision.<sup>47</sup> If the  
608 manufacturing spans multiple time segments (quarters), the started lot should be counted  
609 when the lot number is issued or the API or primary starting material is physically  
610 charged. If unique lot numbers are issued for different packaging configurations, each lot  
611 number should be counted.

612

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<sup>43</sup> See 21 CFR 207.1 (effective November 29, 2016).

<sup>44</sup> See FDA guidance for industry *QIA(R2) Stability Testing of New Drug Substances and Products*.

<sup>45</sup> See 21 CFR 210.3(b)(10).

<sup>46</sup> For example: (1) if the power fails halfway through a tableting operation and a portion of the manufactured tablets are acceptable to release for distribution, this is considered an accepted lot, (2) if an API lot is reworked and released under the original lot number, the lot is considered an accepted lot, (3) for continuous manufacturing, if there was an unplanned shut down of the line due to quality reasons, this would not be considered an accepted lot, (4) if the entire lot is rejected due to an OOS, the lot would not be considered an accepted lot, and (5) if the entire lot is rejected due to a potential contamination, the lot would not be an accepted lot.

<sup>47</sup> See 21 CFR 211.101.

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613 **Lot Release Test** – includes all tests of conformance to final specifications, including all real  
614 time release tests, and all in-process tests that act as a surrogate for final lot release (e.g., real  
615 time release testing is approved in the application).<sup>48,49</sup>

616  
617 **Out-of-Specification (OOS) Result** – all test results that fall outside the specifications or  
618 acceptance criteria established in drug applications, drug master file, official compendia, or by  
619 the manufacturer.<sup>50</sup> An investigation must be conducted whenever an OOS result is obtained.<sup>51</sup>  
620 For the purpose of the quality metrics program, the following test events should be counted: (1)  
621 lot release, including in-process tests that act as a surrogate for a lot release test,<sup>52</sup> and long-term  
622 stability test results *only* and, (2) all lot release and long-term stability test results, even if the  
623 source of the OOS is later determined to be due to a measurement aberration.<sup>53</sup>

624  
625 **Invalidated OOS** – any out-of-specification result where the investigation identifies the  
626 source of the OOS result as an aberration of the measurement process. Invalidation of a  
627 discrete test result may be done only upon the observation and documentation of a test  
628 event that can reasonably be determined to have caused the OOS result.<sup>54</sup> For the  
629 purpose of the quality metrics program, the following test events should be included: (1)  
630 lot release<sup>55</sup> and stability test results *only* and, (2) all lot release and stability test results  
631 that initially appear as OOS, even if invalidated by a subsequent laboratory investigation.

632  
633 **Periodic Product Review** – an evaluation, conducted at least annually, of the quality standards  
634 of a drug product to determine the need for changes in drug product specifications or  
635 manufacturing or control procedures.<sup>56</sup>

636  
637 **Product Family** – for finished drug products, any combination of National Drug Code (NDC)  
638 product code segments where the API and FDF is the same (i.e., a product family could be  
639 multiple strengths or only a single strength).<sup>57</sup> For APIs, the product family is defined by the  
640 NDC product code segment. A product family is defined for the purpose of grouping non-  
641 application drugs for the submission of quality metric data. Grouping is likely consistent with  
642 how products are grouped for the Periodic Product Review (e.g., Annual Product Review).<sup>58</sup>

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<sup>48</sup> See 21 CFR 211.165.

<sup>49</sup> This term does not refer to samples and protocols under 21 CFR 610.2.

<sup>50</sup> See FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.

<sup>51</sup> See 21 CFR 211.192 and section 501(a)(2)(B) of the FD&C Act.

<sup>52</sup> For example, if a near infrared (NIR) spectroscopy-based method is approved for testing active content of core tablets for release as an alternative to testing active content on finished tablets by traditional high-performance liquid chromatography (HPLC) method, and the NIR result is reported on the Certificate of Analysis, this test should be counted as a single analytical result and OOS result, as appropriate, for the purpose of this guidance.

<sup>53</sup> Each test may also be defined as a single analytical result listed on the Certificate of Analysis.

<sup>54</sup> See 21 CFR 211.160(a) and FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.

<sup>55</sup> This term does not refer to samples and protocols under 21 CFR 610.2.

<sup>56</sup> See 21 CFR 211.180(e).

<sup>57</sup> See 21 CFR 207.35.

<sup>58</sup> See 21 CFR 211.180(e).

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643

644 **Product Quality Complaint** – a complaint involving any possible, including actual, failure of a  
645 drug to meet any of its specifications designed to ensure that any drug conforms to appropriate  
646 standards of identity strength, quality, and purity.<sup>59</sup>

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<sup>59</sup> See, e.g., 21 CFR 211.160(b); 211.198.

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647 **APPENDIX A: APPLICABLE IDENTIFYING INFORMATION AND QUALITY**  
648 **METRIC DATA ELEMENTS FOR PRODUCT REPORTS AND SITE REPORTS**  
649

650 This appendix provides clarity on which identifying information and quality metric data elements  
651 are applicable for submission in the voluntary phase of the quality metrics reporting program.  
652 Technical details of quality metric data submissions are provided in the Technical Conformance  
653 Guide.<sup>60</sup> Data standards are available for certain identifying information elements (e.g., dose  
654 forms, business operations).<sup>61</sup>

655  
656 Appendix A is separated into eight (8) subparts. Each subpart corresponds to a different  
657 combination of report type, establishment type, and product type, as described in this draft  
658 guidance. Specifically:

- 659
- 660 • Product Report, segmented by all sites<sup>62</sup>
    - 661 ○ Application Product
      - 662 ▪ Finished Drug Product: Appendix A.1
      - 663 ▪ API: Appendix A.2
    - 664 ○ Non-Application Product
      - 665 ▪ Finished Drug Product: Appendix A.3
      - 666 ▪ API: Appendix A.4
  - 667
  - 668 • Site Report, segmented by products
    - 669 ○ Manufacturing with product quality oversight responsibilities only: Appendix A.5
    - 670 ○ Manufacturer with testing responsibilities: Appendix A.6
    - 671 ○ Manufacturer without testing responsibilities: Appendix A.7
    - 672 ○ Manufacturer with testing responsibilities only: Appendix A.8

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<sup>60</sup> See <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM508464.pdf>.

<sup>61</sup> See <http://www.fda.gov/forindustry/datastandards/structuredproductlabeling/ucm162038.htm>.

<sup>62</sup> For a product report, when information was not provided by a contract facility, the corresponding data elements should be marked as “not provided.”

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*Appendix A.1: Applicable Inputs for a Product Report Submission, Application Product, Finished Drug Product*

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Product Reporting Establishment [Manufacturing with oversight responsibilities only]	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Contract Manufacturer performing release or stability testing	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Contract Manufacturer not performing release or stability testing (FDF, packaging, sterilizing, etc.)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Contract Laboratory performing release or stability testing only	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

675 X = Input is applicable to report; N/A = Input is not applicable to report



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### Appendix A.2: Applicable Inputs for a Product Report Submission, Application Product, API

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Product Reporting Establishment [Manufacturing with oversight responsibilities only]	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Contract Manufacturer performing release or stability testing	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Contract Manufacturer not performing release or stability testing (FDF, packaging, sterilizing, etc.)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Contract Laboratory performing release or stability testing only	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

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X = Input is applicable to report; N/A = Input is not applicable to report

**Contains Nonbinding Recommendations**

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*Appendix A.3: Applicable Inputs for a Product Report Submission, Non-application Product, Finished Drug Product*

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Product Reporting Establishment [Manufacturing with oversight responsibilities only]	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Contract Manufacturer performing release or stability testing	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Contract Manufacturer not performing release or stability testing (FDF, packaging, sterilizing, etc.)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Contract Laboratory performing release or stability testing only	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

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X = Input is applicable to report; N/A = Input is not applicable to report

**Contains Nonbinding Recommendations**

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*Appendix A.4: Applicable Inputs for a Product Report Submission, Non-application Product, API*

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Product Reporting Establishment [Manufacturing with oversight responsibilities only]	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Contract Manufacturer performing release or stability testing	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Contract Manufacturer not performing release or stability testing (FDF, packaging, sterilizing, etc.)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Contract Laboratory performing release or stability testing only	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

684 X = Input is applicable to report; N/A = Input is not applicable to report

**Contains Nonbinding Recommendations**

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*Appendix A.5: Applicable Inputs for a Site Report Submission, Manufacturer with oversight responsibilities only (e.g., application holder)*

	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Finished Drug Product – Application	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
Finished Drug Product – Non-application	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	X	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
API – Application	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A
API – Non Application	X	N/A	X	X	N/A	N/A	N/A	X	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	X	X	N/A	N/A	N/A

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X = Input is applicable to report; N/A = Input is not applicable to report

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697 *Appendix A.6: Applicable Inputs for a Site Report Submission, Manufacturer that perform testing*  
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	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Finished Drug Product – Application	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
Finished Drug Product– Non-application	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
API – Application	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X
API – Non Application	X	N/A	X	X	N/A	N/A	N/A	X	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X

X = Input is applicable to report; N/A = Input is not applicable to report

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*Appendix A.7: Applicable Inputs for a Site Report Submission, Manufacturer that does not perform testing*

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	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Finished Drug Product–Application	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
Finished Drug Product–Non-application	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
API – Application	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A
API – Non Application	X	N/A	X	X	N/A	N/A	N/A	X	X	X	X	N/A	X	X	X	X	X	X	X	X	X	X	N/A	N/A	N/A

X = Input is applicable to report; N/A = Input is not applicable to report

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715 *Appendix A.8: Applicable Inputs for a Site Report Submission, Manufacturer with Testing Only*  
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	Product Name	Rx/OTC	OTC Monograph	Product Type	Applicant Name	Application Type	Application Number	NDC Product Code Number(s)	Reporting Time Period	Quarter	Dose Form	Active Ingredient	Supply Chain/Process Stage Code	FEI/DUN	Started: In-process/Packaging	Started: Saleable	Rejected: In-process/Packaging	Rejected: Saleable	Released: In-process/Packaging	Released: Saleable	Number of quality complaints	Number of Dosage Units Distributed	Sum of Release test and Stability test OOS results where the source of the OOS result is identified as an aberration of the measurement process	Sum of Release test and Stability test OOS results	Sum of all Release and Stability Tests
Finished Drug Products–Application	X	X	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X
Finished Drug Product – Non-application	X	X	X	X	N/A	N/A	N/A	X	X	X	X	X	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X
API – Application	X	N/A	N/A	X	X	X	X	N/A	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X
API – Non Application	X	N/A	X	X	N/A	N/A	N/A	X	X	X	X	N/A	X	X	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	X	X	X

717 X = Input is applicable to report; N/A = Input is not applicable to report

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### 718 **APPENDIX B: EXAMPLES**

719

#### 720 (1) Lot Acceptance Rate

721 a. An establishment manufactures a product where six small in-process lots are  
722 combined into a single unit operation to make one saleable lot (e.g., tablet, liquid,  
723 filled vial). Two saleable lots are then combined into one packaging lot.

724 Assuming all lots that are started are released:

725       ▪ In-process and packaging lots started and released: 13 [six lots from the  
726 first saleable lot, six lots from the second saleable lot, and the single  
727 packaging lot]

728       ▪ Saleable lots started and released: 2

729 b. An establishment manufactures one saleable lot that is separated into five  
730 packaged lots.

731 Assuming all lots that are started are released:

732       ▪ In-process and packaging lots started and released: 5

733       ▪ Saleable lots started and released: 1

734 c. For an OTC monograph product, one batch of saleable product is packaged into  
735 an unlabeled primary pack and the primary pack is subsequently labeled and  
736 placed into secondary packaging at three different packagers. In this scenario, all  
737 four of these facilities are considered covered establishments (one for the bulk  
738 manufacturing and three for primary labeling). For the manufacturer of the  
739 unlabeled primary pack OTC product, the unlabeled primary pack lots are  
740 saleable lots. The lots which are distributed by each packaging establishment are  
741 also saleable lots.

742 d. Facility A manufactures the product and Facility B packages the product. Facility  
743 B discovers a defect that leads to the rejection of the lot; the defect was due to the  
744 manufacturing at Facility A. In this situation, Facility A should not count this  
745 product lot as a released lot, despite the initial release. For Facility B, if the  
746 defect was discovered upon incoming acceptance testing and the packaging lot  
747 was not yet started, the lot should not be counted. If a packaging lot was started,  
748 it should be counted as a lot started, not as a released lot.

749 e. For a non-functional or functional film-coated tablet where the coating process  
750 consists of multiple separate coating pan loads, the count of lots depends on  
751 whether the separate pan loads are considered unique lots or if the loads are part



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752 of a single started lot. For either functional or non-functional coatings, samples  
753 collected and testing for finished drug product release should be representative of  
754 the lot.

755 f. Facility A initiates manufacturing of Product Z in the last quarter of the reporting  
756 cycle or ceases manufacturing of Product Y in the first quarter of the reporting  
757 cycle. An explanation of the partial year can be described in the comment field.  
758 The product report or site report would be considered complete for that product.

### 759 (2) Product Quality Complaint Rate

760 a. If a lot is distributed to five customers and all customers report the same  
761 complaint, this should be counted as five complaints.

762  
763 b. If a lot is distributed and a single customer submits the same complaint from  
764 different departments, only a single complaint should be counted. If submitting a  
765 site report, the covered establishment may choose to include this complaint in  
766 their data if it is the least burdensome option.

767  
768 c. A lot is distributed to three regions and a complaint is received on that lot from a  
769 region outside of the United States. In this instance, the complaint does not need  
770 to be reported as part of the quality metrics program. The covered establishment  
771 may choose to include this complaint if it could be applicable to product imported  
772 or intended for import to the United States or its territories.

773  
774 d. For a site report by a packager, if a complaint is received and potentially due to  
775 the packager's operations (e.g., discolored tablet or powder), the complaint should  
776 be counted by the site reporting establishment.

### 777 778 (3) Invalidated Out of Specification (OOS) Result Rate

779 a. Regarding analytical tests with multiple sample preparations or injections  
780 involved in the test to generate the final result, one test is represented by a single  
781 analytical result with an established limit. For example, one content uniformity  
782 test proceeding to stage two may have 30 invalidated results. Only one OOS  
783 result would be counted.

784  
785 b. If two samples from one lot are tested with two injections each and there is one  
786 result reported on the Certificate of Analysis, this is considered one release test.

787  
788 c. If an OOS result occurs during in-process testing for a test that is considered a  
789 real time release test, this is considered a release OOS result for the purpose of  
790 this guidance.

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- 791 d. If more than one OOS result is observed during finished drug product testing  
792 (e.g., the lot fails both assay and uniformity), this is considered multiple release  
793 OOS results.
- 794 e. 50 kg of an API is packaged into five 10 kg packages and three to five of the five  
795 containers are tested; the Certificate of Analysis reports the average. If one or  
796 more of the container results is OOS for the same attribute, the establishment  
797 should initiate an OOS investigation and count these OOS results as a single OOS  
798 result. A single API container with an OOS result should result in an  
799 investigation for the lot in its entirety. After the investigation is complete,  
800 subsequent retesting should be counted as a new release test.
- 801 f. Company A does not declare an OOS result until the laboratory investigation  
802 proves the result is valid.<sup>63</sup> If invalid, and the original result is not labeled as an  
803 OOS, there will be no record of invalidating an OOS result, thus resulting in a  
804 lower Invalidated OOS Rate for Company A. For the purpose of the quality  
805 metrics program, a lot release OOS result should be counted prior to the  
806 laboratory investigation, in accordance with the term “OOS result” as defined in  
807 this guidance. Furthermore, these type of results should be evaluated as part of  
808 the PPR to determine the need for changes in drug product specifications or  
809 manufacturing or control procedures.<sup>64</sup>

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<sup>63</sup> It should be noted that this practice is inconsistent with the recommendations outlined in FDA guidance for industry *Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production*.

<sup>64</sup> Refer to 21 CFR 211.180(e).