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# Quality Considerations for Continuous Manufacturing 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## ***DRAFT GUIDANCE***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)**

**February 2019  
Pharmaceutical Quality/CMC  
Pharmaceutical Quality/Manufacturing Standards (CGMP)**

# Quality Considerations for Continuous Manufacturing Guidance for Industry

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***Contains Nonbinding Recommendations***

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1 **Quality Considerations for Continuous Manufacturing**  
2 **Guidance for Industry<sup>1</sup>**  
3

4  
5 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
6 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
7 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
8 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
9 for this guidance as listed on the title page.  
10

11  
12  
13 **I. INTRODUCTION**  
14

15 This guidance provides information regarding FDA’s current thinking on the quality  
16 considerations for continuous manufacturing of small molecule, solid oral drug products that are  
17 regulated by the Center for Drug Evaluation and Research (CDER). The guidance describes  
18 several key quality considerations and provides recommendations for how applicants should  
19 address these considerations in new drug applications (NDAs), abbreviated new drug  
20 applications (ANDAs), and supplemental NDAs and ANDAs, for small molecule, solid oral drug  
21 products that are produced via a continuous manufacturing process. FDA supports the  
22 development and implementation of continuous manufacturing for drug substances and all  
23 finished dosage forms where appropriate, including those submitted in NDAs, ANDAs, drug  
24 master files (DMFs), biologics license applications (BLAs), and nonapplication over-the-counter  
25 (OTC) products. Scientific principles described in this guidance may also be applicable to  
26 continuous manufacturing technologies used for these drugs. However, this guidance is not  
27 intended to provide recommendations specific to continuous manufacturing technologies used  
28 for biological products under a BLA.  
29

30 For purposes of this guidance, FDA considers “continuous manufacturing” to be a process in  
31 which the input material(s) are continuously fed into and transformed within the process, and the  
32 processed output materials are continuously removed from the system.<sup>2</sup> Although this  
33 description can be applied to individual unit operations or a manufacturing process consisting of  
34 a series of unit operations, as described in this guidance, continuous manufacturing is an  
35 integrated process that consists of a series of two or more unit operations.  
36

37 This guidance focuses on scientific and regulatory considerations that are specific or unique to  
38 continuous manufacturing. These considerations include process dynamics, batch definition,  
39 control strategy, pharmaceutical quality system, scale-up, stability, and bridging of existing batch  
40 manufacturing to continuous manufacturing. Recommendations broadly applicable to both

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<sup>1</sup> This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> “The system” is the integrated process that consists of a series of two or more unit operations.

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41 continuous and batch processes are generally not covered in this guidance and the reader should  
42 refer to other FDA and International Council on Harmonization (ICH) guidance documents for  
43 such information.

44  
45 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
46 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
47 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
48 the word *should* in Agency guidances means that something is suggested or recommended, but  
49 not required.

## 51 **II. BACKGROUND**

52  
53 FDA is committed to supporting and enabling pharmaceutical innovation and modernization as  
54 part of the Agency’s mission to protect and promote public health. The Agency hopes that these  
55 efforts may also help reduce the number of drug shortages, as noted in FDA’s drug shortage  
56 strategic plan.<sup>3</sup> In 2002, FDA launched an initiative entitled “Pharmaceutical CGMPs for the  
57 21st Century: A Risk-Based Approach,” to encourage the implementation of a modern, science-  
58 and risk-based pharmaceutical quality assessment system.<sup>4</sup> One goal of the initiative is to ensure  
59 that regulatory review, compliance, and inspection policies continue to support continuous  
60 improvement and innovation in the pharmaceutical manufacturing industry. Since publication of  
61 that initiative document, FDA has promoted a vision of a maximally efficient, agile, flexible  
62 manufacturing sector that reliably produces high-quality drug products without extensive  
63 regulatory oversight.

64  
65 FDA supports the adoption of modern manufacturing technology as a foundation for improving  
66 the overall quality of products and availability to patients. FDA recognizes that continuous  
67 manufacturing is an emerging technology that can enable pharmaceutical modernization and  
68 deliver potential benefits to both industry and patients. Continuous manufacturing can improve  
69 pharmaceutical manufacturing by, for example, using an integrated process with fewer steps and  
70 shorter processing times; requiring a smaller equipment footprint; supporting an enhanced  
71 development approach (e.g., quality by design (QbD) and use of process analytical technology  
72 (PAT) and models); enabling real-time product quality monitoring; and providing flexible  
73 operation to allow scale-up, scale-down, and scale-out to accommodate changing supply  
74 demands. We also expect that this operational flexibility may decrease the need for some  
75 postapproval regulatory submissions. Therefore, FDA expects that adopting continuous  
76 manufacturing for pharmaceutical production will reduce drug product quality issues, lower  
77 manufacturing costs, and improve availability of quality medicines to patients.

78  
79

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<sup>3</sup> See FDA’s Strategic Plan for Preventing and Mitigating Drug Shortages (October 2013) at:  
<https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf>.

<sup>4</sup> See Pharmaceutical cGMP’s for the 21st Century: A Risk-Based Approach (September 2004) at:  
<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/manufacturing/questionsandanswersoncurrentgoodmanufacturingpracticescgmppfordrugs/ucm176374.pdf>.

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### 80 **III. QUALITY CONSIDERATIONS**

81

#### 82 **A. Key Concepts of Continuous Manufacturing**

83

##### 84 *1. Process Dynamics*

85

86 Product and process understanding form the foundation for effective risk management.<sup>5</sup> The  
87 expectations regarding the science- and risk-based approach to the control of processes and  
88 product quality based on process understanding are the same for continuous manufacturing as for  
89 traditional batch manufacturing.<sup>6</sup>

90

91 Continuous manufacturing processes are dynamic systems, unlike batch manufacturing  
92 processes. During normal operation, a set of critical process parameters and/or quality attributes  
93 are kept close to the target values, rather than at a steady-state condition. Transient disturbances  
94 may occur during normal operation. These are usually small enough to be controllable (i.e.,  
95 being kept within a desired range). Larger changes in process parameters and quality attributes  
96 can happen when a process is in a transient state, such as during start-up and shutdown, a change  
97 from one operating condition to another, or significant deviations such as those due to equipment  
98 failure or unexpected change in material attributes. Understanding of process dynamics as a  
99 function of input material attributes (e.g., potency, material flow properties), process conditions  
100 (e.g., mass flow rates) or equipment design elements (e.g., blade types for a continuous blender)  
101 enables material traceability (the ability to preserve and access the identity and attribute of a  
102 material throughout the system) during and after production. This knowledge is essential for  
103 identification and mitigation of risks to product quality. Therefore, due to the dynamic nature of  
104 continuous processing, the risk assessment for a continuous manufacturing process should  
105 consider process understanding of the integrated system in addition to each unit operation.

106

107 A suitable scientific approach should be used to characterize how a material flows through the  
108 process. One common approach is characterization of residence time distribution (RTD) for the  
109 individual unit operations and integrated system. An RTD is a probability distribution that  
110 describes the amount of time a mass or fluid element remains in a process, and can be measured  
111 through a tracer experiment, online process measurements of appropriate product attributes,  
112 and/or process modeling. The shape of the RTD reflects the degree of axial dispersion or back  
113 mixing within that system, which affect the propagation of disturbances, material traceability,  
114 and the control strategy (e.g., material diversion and sampling frequency). The RTD is dependent  
115 upon several factors such as input material attributes, mass flow rates, process parameters, and  
116 equipment design and operation. It is important to understand how the RTD varies over the range  
117 of planned operating conditions in addition to characterizing the RTD at the nominal/target  
118 operating conditions. This information serves as a basis for material traceability and

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<sup>5</sup> See guidance for industry *Q9 Quality Risk Management* (June 2006) and *Q10 Pharmaceutical Quality System* (April 2009).

<sup>6</sup> See *Pharmaceutical cGMP's for the 21st Century: A Risk-Based Approach* (September 2004) at:  
<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/manufacturing/questionsandanswersoncurrentgoodmanufacturingpracticescgmppfordrugs/ucm176374.pdf>.

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119 determination of appropriate sampling plans and is essential to designing a control strategy for  
120 continuous manufacturing processes.

121

### 122 2. *Defining Batches for Continuous Manufacturing Processes*

123

124 The definition of a batch has regulatory implications, particularly with respect to current good  
125 manufacturing practice (CGMP), product recalls, and regulatory decisions. The terms *batch* and  
126 *lot* are defined in the regulations (21 CFR 210.3) as follows:

127

128 • Batch means a specific quantity of a drug or other material that is intended to have  
129 uniform character and quality, within specified limits, and is produced according to a  
130 single manufacturing order during the same cycle of manufacture.

131 • Lot means a batch, or a specific identified portion of a batch, having uniform  
132 character and quality within specified limits; or, in the case of a drug product  
133 produced by continuous process, it is a specific identified amount produced in a unit  
134 of time or quantity in a manner that assures its having uniform character and quality  
135 within specified limits.

136

137 These definitions for both batch and lot are applicable to continuous manufacturing. A batch can  
138 be defined based on the production period, quantity of material processed, quantity of material  
139 produced or production variation (e.g., different lots of incoming raw material), and can be  
140 flexible in size to meet variable market demands by leveraging the advantage of operating  
141 continuously over different periods of time. A lot may also be considered a sub-batch. The actual  
142 batch or lot size should be established prior to the initiation of each production run.

143

144 For batches that are defined based on time (e.g., a production period), a connection between  
145 material traceability and batch must be established to identify the specific quantity of the drug  
146 (21 CFR 210.3).

147

### 148 **B. Control Strategy**

149

150 Establishing, maintaining, and refining a control strategy is a life cycle activity – from  
151 development to technology transfer to ongoing verification during the commercial manufacturing  
152 phase – and is supported by pharmaceutical development, quality risk management, and a robust  
153 pharmaceutical quality system (PQS). An effective PQS strengthens the links across the stages of  
154 a product’s life cycle and enables the development and continuous improvement of the control  
155 strategy.<sup>7</sup> This section provides considerations for the control strategy in the framework of a  
156 robust PQS for a continuous manufacturing process.<sup>8</sup>

157

---

<sup>7</sup> See guidances for industry *ICH Q8 (R2) Pharmaceutical Development* (November 2009), *ICH Q9 Quality Risk Management* (June 2006), and *ICH Q10 Pharmaceutical Quality Systems* (April 2009). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>8</sup> Refer to 21 CFR 211 subpart F, Production and Process Controls for related regulations.

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158 In general, in developing a *control strategy*,<sup>9</sup> manufacturers should consider unexpected and  
159 expected variations. For continuous manufacturing processes, this is even more critical, as there  
160 may be transient disturbances in input material attributes, process conditions, or environmental  
161 factors over time during normal operation. An effective control strategy for this continuous mode  
162 of operation should place special emphasis on mitigating the risk of these potential disturbances  
163 to product quality. To maintain a process within a state of control during continuous operation,  
164 detect temporary process disturbances, and segregate the resulting nonconforming materials from  
165 the system, manufacturers should increase the use of in-process control strategy elements.

166  
167 The following describes recommendations for key aspects of the control strategy for a  
168 continuous manufacturing process.

### 169 170 *1. Input Material Control*

171  
172 In a continuous manufacturing process, input materials are continuously added through a feeder  
173 system (e.g., loss-in-weight feeders for solid powders or pumps for liquids) over the duration of a  
174 production run. Different batches of input materials can be introduced to the system at different  
175 process time points, and variability in input material attributes could affect feeding, introduce  
176 process variability into the system, impact RTD models, and potentially affect finished product  
177 quality. In addition, transport processes in the integrated system may cause some degree of  
178 transformation (e.g., segregation or aggregation of powders). Therefore, continuous  
179 manufacturing may warrant additional characterization and control of input material attributes  
180 beyond compendial standards. Suitable risk analyses, experimental investigation, and/or  
181 modeling and simulation should be considered throughout the life cycle of the product, including  
182 during pharmaceutical development, to evaluate potential impact of material attributes (e.g.,  
183 particle size distribution and density of the active pharmaceutical ingredient (API) and  
184 excipients) on the material flow properties, process dynamics, and quality of a final product over  
185 the period of an intended production run.

186  
187 A formal monitoring program can be useful for manufacturers to identify changes in high risk  
188 raw material properties (e.g., inter-batch, intra-batch, and shifts over time) and proactively  
189 identify and mitigate the impact of these changes on the manufacturing process and the finished  
190 drug product.

191  
192 Manufacturers planning to switch from batch to continuous manufacturing should take a similar  
193 approach to re-evaluate the existing specification(s) for raw materials and their use in a particular  
194 continuous process design.

### 195 196 *2. Process Monitoring and Control*

197  
198 Implementation of a well-justified process monitoring approach is an element of the control  
199 strategy for any drug manufacturing process. For continuous manufacturing processes, process

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<sup>9</sup> See guidance for industry *ICH Q8 (R2) Pharmaceutical Development* (November 2009) for the definition of *control strategy*.



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200 monitoring and utilization of PAT tools<sup>10</sup> generate real time information on process parameters  
201 and attributes of input materials, in-process materials, and final products for the duration of the  
202 manufacture. This information can enable high detectability of transient disturbances and process  
203 deviations, active process control, more accurate material diversion, and real time release testing  
204 (RTRT).<sup>11</sup> A process monitoring approach should include at least the following:  
205

- 206 • Variables being monitored at appropriate locations in the process, such as:
  - 207 ○ Process parameters,
  - 208 ○ Input and in-process material attributes, and
  - 209 ○ Final product attributes.
- 210
- 211
- 212 • Sampling plan, including:
  - 213 ○ Sampling locations,
  - 214 ○ Sampling or measurement frequency,
  - 215 ○ The sample size to be taken and measured, and
  - 216 ○ Statistical criteria appropriate for use to evaluate the process monitoring data.
- 217
- 218
- 219 • Type of analyses for process monitoring data, such as:
  - 220 ○ Univariate analysis based on control limits,
  - 221 ○ Multivariate or process model, and
  - 222 ○ Inter- and intra-batch trend analysis (e.g., moving averages and variance analysis).
- 223
- 224
- 225 • Intended use(s) of process monitoring data, such as:
  - 226 ○ Supporting other control strategy elements (e.g., active process control, material
  - 227 diversion, RTRT, batch release),
  - 228 ○ Evaluating process and equipment performance as part of process development,
  - 229 during manufacturing, and to facilitate continued process verification,
  - 230 ○ Ongoing monitoring of a process to confirm that it remains under a state of
  - 231 control, and
  - 232 ○ Additional elements of the Pharmaceutical Quality System.<sup>12</sup>
- 233
- 234

235 Developing the measurement system and sampling plan for process monitoring warrants several  
236 considerations. To determine which variables need to be monitored, the relationships linking  
237 material attributes and process parameters to product critical quality attributes (CQA) should be

---

<sup>10</sup> For details regarding PAT tools, refer to guidance for industry *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (September 2004). The PAT tools described in this guidance encompass spectroscopic and chemometric tools as well as non-spectroscopic sources and soft sensors. ASTM E2629 Standard Guide for Verification of Process Analytical Technology (PAT) Enabled Control Systems may be another useful document.

<sup>11</sup> See guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

<sup>12</sup> Refer to section III.D, Additional Pharmaceutical Quality System Considerations.

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238 understood.<sup>13</sup> The sampling plan should consider the intended use of process monitoring data  
239 and the impact of process dynamics on measurement frequency. The measurement equipment  
240 (e.g., the location of a sensor) should be evaluated to achieve representative sampling and avoid  
241 interference with the process.  
242

243 Development of the process monitoring approach should include a risk assessment that includes  
244 consideration of how lapses in process monitoring data collection (e.g., recalibrating a near  
245 infrared (NIR) probe or refilling a feeder) might affect product quality.<sup>14</sup> The process monitoring  
246 approach selected should include alternative or additional quality controls to mitigate the risks  
247 to product quality posed by these scenarios.  
248

249 Active process control requires that some parameters in the system have the capability to be  
250 adjusted in real time to reduce the risk of producing nonconforming materials. In this context,  
251 predefined process adjustments would not necessarily represent a departure from a state of  
252 control. An approach that includes implementation of active process control can include operator  
253 actions, increased sampling frequency, and automated feedforward/feedback controls, among  
254 other strategies. The establishment of appropriate limits (e.g., alarm or action limits) is also  
255 important for robust process control. The limits of acceptability for controls that ensure  
256 monitored critical process parameters and critical material attributes stay within desired ranges  
257 should be specified in the regulatory submission.  
258

### *3. Material Diversion*

259  
260  
261 A continuous manufacturing process is expected to maintain a state of control<sup>15</sup> and produce a  
262 product with desired quality. However, the manufacturing process will include periods when  
263 nonconforming material is produced, such as during start-up, shutdown, or temporary process  
264 disturbances. If the approaches for material traceability (see section A.1), process monitoring  
265 (see section B.2), and material removal are well established, this nonconforming material can be  
266 segregated and removed without affecting the rest of the batch.  
267

268 In a period when nonconforming material is produced, the amount of diverted material should  
269 depend on the duration and severity of the disturbance, system process dynamics, and location of  
270 a diversion point. Studies of process dynamics, including RTD and disturbance propagation  
271 through the process, form the basis for determining the appropriate amount of material for  
272 diversion. The design of the system should consider including diversion points at  
273 commencement or completion of significant phases of production.<sup>16</sup> Design of the diversion  
274 point(s) locations should also consider feasibility of removal of material, the effect of location on  
275 the amount of material affected (e.g., dispersion of nonconforming materials via back-mixing or  
276 material transformation in the subsequent steps), and the effect of nonconforming material on

---

<sup>13</sup> See guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

<sup>14</sup> See guidance for industry *Q9 Quality Risk Management Development* (June 2006).

<sup>15</sup> For the definition of *state of control*, see guidance for industry *ICH Q10 Pharmaceutical Quality System* (April 2009).

<sup>16</sup> See 21 CFR 211.110(c).

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277 downstream processing. The establishment of safety margins to prevent nonconforming material  
278 from collection with acceptable material is recommended.

279  
280 The manufacturer should establish procedures describing when material identified as potentially  
281 nonconforming is to be diverted and collected. If material is diverted due to an unexplained  
282 discrepancy, the reason for the discrepancy must be appropriately investigated before  
283 dispositioning the batch.<sup>17</sup> Diversions that are the result of expected system operating conditions  
284 may not require an investigation under 21 CFR 211.192. When frequent or cyclical process  
285 disturbances occur within a single production run resulting in atypical low yield,<sup>18</sup> the entire  
286 batch may need to be rejected depending on the outcome of the investigation. As appropriate,  
287 investigations must extend to other potentially affected batches and products.<sup>19</sup>

### 288 289 4. Real Time Release Testing

290  
291 Monitoring of a continuous manufacturing process using PAT tools can generate a large amount  
292 of real-time process and quality data during production, which can be used to support RTRT.  
293 Although RTRT is not a regulatory requirement for implementation of continuous manufacturing  
294 processes, it is encouraged and could be applied to some or all of the finished product quality  
295 attributes tested for release of the batch.

296  
297 When the RTRT is adopted as a part of the control strategy, special considerations should be  
298 given to the sampling strategy. The implementation of RTRT includes in-process online, at-line,  
299 and/or inline sampling. The selected sample size or frequency should be representative of the  
300 batch and the approach should be justified using an appropriate statistical approach with respect  
301 to the quality assurance provided by the specific approach (e.g., confidence and coverage). For  
302 data collected at high frequency, statistical methods for large sample sizes should be applied to  
303 provide improved characterization of a batch. RTRT calculations should also consider the  
304 observed variance in CQAs over a multi-batch campaign to account for both intra- and inter-  
305 batch variability. Furthermore, procedures should be developed to establish a plan for RTRT to  
306 address potential gaps in PAT data (e.g., failure of the PAT equipment).

307  
308 Models can also be used to support RTRT. The models used for RTRT are regarded as high  
309 impact models, as per the criteria outlined in the *Role of Models in Quality by Design (QbD)*  
310 section in the *ICH QIWG Points to Consider* document.<sup>20</sup> Examples of these models can include  
311 multivariate models to predict dissolution for release and calibration models associated with NIR  
312 procedures that are used for content uniformity and assay release testing. The *ICH QIWG Points*  
313 *to Consider* document provides guidance on the development, validation, life cycle maintenance,  
314 and documentation for the high impact models.

315

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<sup>17</sup> See 21 CFR 211.192.

<sup>18</sup> As with batch manufacturing, yield should be used as one criterion for determining whether the investigation of an entire batch is needed.

<sup>19</sup> See 21 CFR 211.192.

<sup>20</sup> See ICH QIWG Points to Consider (12/6/2011),

[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Quality/Q8\\_9\\_10\\_QAs/PtC/Quality\\_IWG\\_PtCR2\\_6dec2011.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf).

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316 The following are examples of quality attributes and considerations for RTRT implementation:  
317

- 318 • Identity testing of finished products  
319
  - 320 ○ The identity test should be capable of distinguishing between other products  
321 manufactured at the manufacturing facility.
  - 322 ○ The impact of any unique identifiers such as embossing and sample orientation on  
323 the test method should be examined.
  - 324 ○ If the identity test is performed on an intermediate instead of the finished product,  
325 controls should be in place to prevent potential human and/or system errors during  
326 the subsequent processing steps.  
327
- 328 • Tablet assay and content uniformity by NIR<sup>21</sup>  
329
  - 330 ○ The sample size and sampling frequency for the NIR measurement should be  
331 statistically justified to provide adequate quality assurance.
  - 332 ○ The measurement location should be representative of the finished tablet and  
333 minimize the potential for segregation to occur (e.g., feed frame of the tablet  
334 compression step or uncoated tablet). The NIR measurement of active  
335 concentration in the tablet should account for tablet weight in calculating the total  
336 active concentration in a tablet.
  - 337 ○ The PAT tool used for RTRT should be validated against the offline analytical  
338 method (e.g., High-Performance Liquid Chromatography).
  - 339 ○ The calibration model associated with the NIR method should be adequately  
340 developed and validated over the proposed operating ranges for commercial  
341 production.  
342
- 343 • Model serving as a surrogate for the release test  
344
  - 345 ○ The model should be developed by considering all variables that have the  
346 potential to impact the quality attribute and is typically a function of a relevant  
347 combination of measured material attributes and process parameters.
  - 348 ○ The model should be developed to account for the potential variations in material  
349 attributes and processing conditions expected during commercial production.
  - 350 ○ The model should be validated using a statistically sound approach and against  
351 corresponding release testing method(s), as well as demonstrate specificity (e.g.,  
352 capability of detecting nonconforming product). The sample must pass a  
353 corresponding release testing method, if tested.<sup>22</sup>  
354  
355

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<sup>21</sup> Refer to draft guidance for industry *Development and Submission of Near Infrared Analytical Procedures* (March 2015) at

<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM440247.pdf>.

<sup>22</sup> See 21 CFR 211.165.

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### 356 5. *Specification*

357  
358 Finished product specifications are required for products manufactured in accordance with 21  
359 CFR 314.50(d) and 21 CFR 211.165(a). The approach to establishing specifications for  
360 continuous manufacturing processes should follow ICH Q6A and B with special considerations  
361 given to the sampling approach. As described in the above section, the use of RTRT is  
362 encouraged as it generally incorporates an enhanced sampling plan more representative of the  
363 batch, enabling the manufacturer to use better predictive statistical tools. In the case where  
364 RTRT is adopted in lieu of offline, end product testing, the specification should also include a  
365 regulatory offline analytical method and associated acceptance criteria that will be used to assess  
366 product quality over the shelf life.

### 367 6. *Equipment*

368  
369  
370 Manufacturers using continuous manufacturing processes may need to run equipment for long  
371 periods of time to achieve the predetermined batch size. Equipment performance could decline  
372 gradually during the same run or after several repeated runs, due to fouling or normal wear and  
373 tear. Such a performance decline may not be observed in short development runs. Therefore,  
374 equipment for continuous manufacturing warrants the following additional considerations on  
375 qualification, maintenance, and cleaning.

376  
377 Equipment qualification should address both individual unit operations and the integrated  
378 system. Qualification of the integrated continuous equipment should demonstrate that the  
379 equipment is adequate for its intended purpose.<sup>23</sup> Qualification protocols should be  
380 representative of expected operating conditions including flow rates, pressures, speeds, and the  
381 duration of a continuous run. The quality unit should establish acceptance criteria for equipment  
382 performance and stability (e.g., parameter variability and drifts, as well as the absence of  
383 detrimental events) to support the development and operation of continuous manufacturing  
384 processes. During equipment qualification, the functionality of equipment components should  
385 evaluate specific events, including those used for detection of disturbances and execution of  
386 material diversion (e.g., forced perturbations).

387  
388 Throughout the product life cycle, the development and maintenance of the control strategy  
389 should take into account equipment failure modes to ensure that abnormal equipment  
390 performance is detected and investigated, including appropriate corrective action. Equipment  
391 maintenance and calibration procedures should be developed and updated based on ongoing  
392 monitoring of equipment performance and other available information (e.g., experience with the  
393 equipment, equipment design, knowledge gained during the development and qualification  
394 results). The process monitoring strategy should include indicators of equipment performance  
395 based on qualification experience and understanding of potential failure modes. This can also  
396 help to determine the maximum run time for the integrated line before maintenance or cleaning  
397 is needed.

398

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<sup>23</sup> Refer to 21 CFR 211 subpart D, Equipment.

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399 Cleaning approaches should be developed and defined based on understanding obtained from  
400 development and scale-up (e.g., increased production run time) studies, and then be periodically  
401 verified to confirm continued effectiveness. Cleaning procedures should be established based on  
402 close monitoring of materials during operation and after disassembly, and should include, for  
403 example, examination of material hold up and build up on equipment, piping, filters, and  
404 instruments (e.g., online analyzers and sensors), degradation of material within the processing  
405 line during operation, chemical film formation, and microbial growth. The conditions evaluated  
406 during cleaning validation should take into account the potential failure modes (e.g., fouling)  
407 under the anticipated worst-case scenario (e.g., an extended production run time) based on the  
408 risk to the product quality or the risk of contamination to other products manufactured at the  
409 facility.

410  
411 Batch size and campaigning procedures should be established with consideration of the  
412 maintenance and cleaning requirements for the integrated line. In general, cleaning frequency for  
413 continuous manufacturing processes should be established based on elapsed operating time,  
414 quantity of material processed, history of process conditions or deviations, and product change-  
415 over, if applicable. Preventive maintenance timetables, equipment monitoring, and time and/or  
416 operational limits (e.g., amount of materials being processed) between cleanings should be  
417 periodically evaluated and updated as part of life cycle management.

### *7. System Integration, Data Processing, and Management*

418  
419  
420  
421 For real time process monitoring and decision-making to be feasible, the integrated equipment  
422 and control strategy requires a robust automated platform to orchestrate production. Because of  
423 the speed with which decisions must be made in continuous operation, quality unit oversight  
424 relies heavily on data and actions from the automated system. Therefore, the routine operational  
425 and material disposition decision-making should be integrated into the automated control system.

426  
427 The design and validation of the automation system, as well as its integrated qualification along  
428 with the entire equipment train, are critical. Both process control functionality and quality unit  
429 oversight should be part of the system and software design.<sup>24</sup> Special considerations should be  
430 given when integrating equipment and software from multiple vendors (e.g., consistent coding of  
431 a single parameter tag between systems). During the integrated qualification of the automation  
432 system and manufacturing equipment, it is important to demonstrate the functionality of the  
433 whole system, which could include introducing disturbances or inducing failure modes to ensure  
434 that the system responds as designed.

435  
436 Well-designed software and associated validation, equipment qualification, integration of quality  
437 decision making, and automation maintenance make it possible for a continuous process to

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<sup>24</sup> There are industry standards that are helpful in validating the automation system. For example, see the International Society for Pharmaceutical Engineering (ISPE) Guide for Validation of Automated System (GAMP), or the systems engineering “V-Model” process.

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438 operate with the minimum practical level of operator intervention.<sup>25</sup> As part of the control  
439 strategy, alarms should be implemented in the automation system to ensure that the system  
440 continues to operate within the predefined limits. Action taken in response to alarms should be  
441 commensurate with the severity of the triggering event. The quality unit should determine in  
442 advance the appropriate actions for specific alarms or classes of alarms, which could include, for  
443 example, operator observation, operator intervention, or automated diversion of material.  
444 Standard operating procedures (SOPs) should be established in advance for responding to and  
445 reacting to alarms or alarm classes, as well as for investigating the underlying issue that triggered  
446 the alarm.

447  
448 Electronic data and data systems must comply with 21 CFR parts 11 and applicable sections of  
449 211. Considerations applicable to electronic data may include (but is not limited to) the  
450 following:

- 451
- 452 • Accurate reproduction of the appropriate master production or control record
  - 453 • Documentation that each significant step was accomplished, including but not limited to  
454 in-process results and the identification of the person checking the significant step  
455 performed by the automated equipment
  - 456 • Network security, system integrity/functionality checks, single-user identification, and  
457 audit trails
  - 458 • Software version control, manufacturing batch record version control, and the integrity of  
459 loaded manufacturing process during start-up
  - 460 • Computing speed and capacity, local and remote memory, and communication assurance
  - 461 • Data archiving and recall
  - 462 • Software maintenance and change controls
- 463

464 The automated controls system is likely to be the primary source of batch records for batch  
465 record review of continuous processes. Data reporting and review considerations generated by  
466 the automated controls systems should include (but are not limited to):

- 467
- 468 • Manufacturing batch record: report with initial set-points and ranges and model versions
  - 469 • Actions performed: audit trail (including sub-systems) reports, process parameter and in-  
470 process material attribute control charts, material collection report (documenting the  
471 conditions achieved when material was collected, diverted, or when collection  
472 commenced), and any reports from any other process-specific performance metrics
  - 473 • Deviations: alarm reports, periods of material diversion, and corrective actions reports
  - 474 • Materials: reconciliation and material collected, segregated and diverted report, and  
475 actual and theoretical percent yield
- 476  
477

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<sup>25</sup> For example, per 21 CFR 211.188(b)(11), significant steps performed by the automation must be checked by a human. As such, operator confirmation may be required for critical manufacturing steps (e.g., confirmation of the start of product collection once a state of control has been established).

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### 478 **C. Process Validation**

479  
480 The guidance for industry *Process Validation: General Principles and Practices* and *ICH Q8*,  
481 *Q9*, and *Q10*, is applicable to continuous manufacturing processes. For these types of  
482 manufacturing processes, the ability to evaluate real time data to maintain operations within  
483 established criteria to produce drug products with a high degree of assurance of meeting all the  
484 attributes they are intended to possess is an integral element of process validation. Manufacturers  
485 using continuous manufacturing processes may find that some process validation stages are more  
486 concurrent and interrelated (e.g., process design and equipment qualification) than they are with  
487 batch manufacturing processes. This is, in part, because the development of a continuous  
488 manufacturing process generally uses commercial scale equipment. This offers significant  
489 advantages in that equipment size scale-up issues commonly encountered in the development of  
490 batch manufacturing processes will likely be minimized. Consequently, there may be activities  
491 described below in stages 2 and 3 that may be more appropriate to perform during stage 1. For  
492 example, it may be more appropriate to perform some equipment qualification activities prior to  
493 some stage 1 validation studies as those studies may also be used to demonstrate inter- and intra-  
494 batch variability at commercial scale (i.e., during process performance qualification (PPQ)). That  
495 is, it is important to ensure that the equipment operates properly prior to generating data that  
496 satisfies some of the expectations for PPQ. Furthermore, to better understand inter- and intra-  
497 batch variability, the design of the process monitoring strategy during development should  
498 consider monitoring needs for commercial scale continued process verification throughout the  
499 life cycle of the product (stage 3).

#### 500 501 *1. Stage 1 – Process Design*

502  
503 Stage 1 process design includes designing the process and establishing the control strategy. The  
504 corresponding studies and decision points, including the design of equipment and automation  
505 systems, assessment of input material attributes, process dynamics and variability, development  
506 of strategies or procedures for material diversion, process monitoring and control, and other  
507 control strategy elements, have already been discussed in section III.B. This development  
508 provides a foundational understanding of the manufacturing process and quality expectations for  
509 operation and is essential for enabling verification of process robustness in stage 2.

#### 510 511 *2. Stage 2 – Process Qualification*

512  
513 Qualification of the integrated equipment and automated control systems is essential for ensuring  
514 the performance of a continuous process. Given the interrelated nature of the integrated  
515 equipment, process design, and control strategy, the first component described in stage 2 of the  
516 *Process Validation* guidance, *Design of Facilities and Qualification of Utilities and Equipment*,  
517 may often be more appropriate to perform in stage 1. Additionally, information on the equipment  
518 and automation system performance and its variability will inform the design of the PPQ  
519 protocol. Because the reliable performance of equipment and automation is critical for PPQ,  
520 manufacturers should evaluate whether they have sufficient experience with the fully integrated  
521 continuous manufacturing process before initiating PPQ.

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523 The second part of stage 2 PPQ demonstrates the robustness of the manufacturing process and  
524 adequacy of the control strategy following completion of process development and integrated  
525 equipment-automation qualification. The PPQ protocol should be designed to assess robustness  
526 with respect to the known sources of variability including those unique to continuous  
527 manufacturing processes (e.g., mass flow rate fluctuation from a loss-in-weight feeder) and  
528 should leverage knowledge gained from Process Design and Equipment Qualification.

529  
530 PPQ should also demonstrate the reproducibility of the manufacturing process over time (from  
531 start-up to shutdown and from batch to batch), and therefore manufacturers should establish  
532 measures of process stability and associated acceptance criteria as part of the PPQ protocol.  
533 Equipment performance criteria can be established to identify equipment problems and  
534 deviations that would impugn the adequacy of the equipment design or qualification, versus  
535 those that result from common cause variations. Metrics should be established to assess process  
536 robustness (e.g., parameter stability/variance and the actual yield).

537  
538 The design of the initial PPQ study to examine a run time or manufacturing period should be  
539 representative of the intended commercial run time for the initial product launch. An integrated  
540 continuous manufacturing process may encounter unforeseen sources of variability with  
541 extended run times, such as process drift, equipment fatigue, and material buildup. Stage 1  
542 process understanding and control strategy design and stage 2 equipment qualification  
543 experience can be leveraged to demonstrate that the proposed PPQ run time is sufficient to  
544 accurately capture expected process variability and therefore demonstrate intra-batch process  
545 robustness. Likewise, for processes that are expected to run in campaigns (i.e., consecutive  
546 batches), PPQ should be designed to capture variability associated with campaigning and may  
547 also leverage stages 1 and 2 understanding of these manufacturing extensions, as needed. In later  
548 stages of the product life cycle, additional PPQ studies may be performed to support greater  
549 flexibility in the batch size to enable patient demand to be met more effectively.

550  
551 Sampling plans (online, at-line, or offline) for critical intermediate or finished product quality  
552 attributes during PPQ should be sufficient to verify that consistent quality material is being  
553 produced throughout the run. The magnitude and duration of variability for process parameters  
554 and quality attributes should be evaluated as part of the PPQ protocol, and should be justified.  
555 For batch processes, PPQ will generally have a higher level of sampling, additional testing, and  
556 greater scrutiny of process performance than would be typical of routine commercial production.  
557 Continuous manufacturing processes using high frequency monitoring of process parameters and  
558 quality attributes may not need additional monitoring during PPQ.

559  
560 PPQ should include interventions which would normally occur during the process (e.g., PAT  
561 probe replacement at pre-established intervals, feeder refills, or shift changes). If disturbances do  
562 occur during PPQ, the PPQ study should confirm that the automated system, operations, and the  
563 quality unit are capable of identifying the event, diverting material, and/or making process  
564 corrections, as intended and per established procedures.

565  
566

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### 567 3. *Stage 3 – Continued Process Verification*

568  
569 Continued process verification (CPV) provides continual assurance that the process remains in a  
570 state of control during commercial manufacture. The routine utilization of in-line, on-line, or at-  
571 line measurements employed in continuous manufacturing processes facilitates the ability to  
572 gather, analyze, and trend product and process data.

573  
574 CPV encompasses an ongoing program to collect and analyze product and process data that  
575 relate to product quality.<sup>26</sup> The data collected should include relevant process parameters,  
576 equipment performance indicators, and quality attributes of input materials, in-process  
577 material(s) and finished product. Data analysis and trending should include:

- 579 • Quantitative and statistical methods, including multivariate approaches, whenever  
580 appropriate and feasible;
- 581 • Scrutiny of intra-batch as well as inter-batch variation; and
- 582 • The development, implementation, evaluation, and improvement, as necessary, of a plan  
583 for the frequency of analysis, attributes for examination, and predetermined statistical  
584 criteria for variance.

585  
586 The product and process knowledge gathered through data analysis and trending should be used  
587 to facilitate continued process verification, initiate process improvements (e.g., refining the  
588 control strategy), and support postapproval changes.

#### 589 **D. Additional Pharmaceutical Quality System Considerations**

590  
591 To implement continuous manufacturing in an existing manufacturing facility, the site should  
592 evaluate its PQS and associated elements to determine if the design and programs within the  
593 PQS should be modified. For example, revised or additional procedures may need to be adapted  
594 or established to support a continuous manufacturing process, including:

- 597 • Handling of planned and unplanned process disturbances which occur real-time,  
598 including the associated investigations
  - 599 • Raw and in-process material investigations
  - 600 • In-process material diversion strategy, including the criteria for rejection of the entire  
601 batch
  - 602 • Change management and maintaining an effective corrective action and preventive action  
603 (CAPA) system
  - 604 • PPQ protocol and continued process verification approach, including process robustness,  
605 actual yield, and multivariate tracking and trending
  - 606 • Equipment qualification and maintenance
  - 607 • Use of formal and informal quality risk management principles throughout manufacturing  
608 operations and quality decision-making
- 609

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<sup>26</sup> See 21 CFR 211.180(e).

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610 These PQS considerations may need to be implemented during development to support  
611 knowledge management, development of the control strategy and monitoring plan, and process  
612 validation activities.

613  
614 The manufacturing site should establish an appropriate level of continuous manufacturing  
615 expertise in the quality, pharmaceutical development, manufacturing operations,  
616 equipment/engineering support, and regulatory affairs organizations.<sup>27</sup> It is likely that additional  
617 training would be needed. Where additional training in continuous manufacturing operations is  
618 needed, this training should be sufficient to enable each group to make decisions based on  
619 science, risk, and quality principles.

620  
621 An integrated team approach for many aspects of quality unit decision-making is recommended  
622 as the design and implementation of a continuous manufacturing process is a multi-disciplinary  
623 undertaking. For example, both the quality unit and technical development functions should  
624 provide input on the design of diversion points for nonconforming material and SOPs for  
625 adjusting continuous operations following disturbances.

### **E. Scale-Up**

626  
627  
628  
629 In a typical batch process, scale-up is associated with an increase in equipment size. Continuous  
630 manufacturing processes offer several different modes of scale-up as discussed below. Each  
631 method of scale-up should be carefully examined to identify risks, studies to be conducted to  
632 ensure that the risks are adequately mitigated, and data needed to support the scale-up plan.

633  
634 An advantage of continuous manufacturing is that the equipment used for process development  
635 can be used for commercial manufacturing. When the same equipment is used, a scale increase  
636 can be achieved by the following methods:

- 637
- 638 a. Increasing run time with no change to the mass flow rate – this is usually the simplest  
639 form of scale-up for continuous processes as it requires little change to be made to the  
640 manufacturing process. The risks associated with this method are usually related to the  
641 operation of integrated equipment, analytical instrumentation and computer systems (e.g.,  
642 data storage) over longer periods of time, as well as cleaning. Equipment “dead zones,”  
643 material build up, equipment drift, and transient disturbances that were not observed over  
644 shorter run times may become visible with run time increases.
  - 645  
646 b. Increasing the mass flow rate – a change in the mass flow rate results in a change to the  
647 process dynamics and residence time distribution. Hence, many aspects of the process,  
648 such as process parameters and controls, sampling frequency and size, material  
649 traceability, designated quantity for rejection following a disturbance, batch specific  
650 automation instruction files, and process limiting factors should be evaluated and  
651 adjusted, as appropriate.
- 652

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<sup>27</sup> These considerations remain applicable when establishments choose to use contract manufacturing organizations.

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653 c. Increasing both run time and mass flow rate – the risks associated with both (a) and (b)  
654 would apply.

655  
656 An increase in scale could also be achieved by a scale-out approach where two or more units of  
657 the same equipment are run in parallel. This approach to scale-up may be appropriate when large  
658 increases in scale are desired, or when equipment used for certain unit operations tend to form  
659 bottlenecks due to comparatively long residence times. Challenges with this approach may  
660 include maintaining uniform flow distribution among the parallel units (e.g., reactors), data  
661 acquisition and storage, and material traceability.

662  
663 Some continuous processes may scale-up by increasing equipment size, like a batch  
664 manufacturing process. Engineering principles of scale-up should be carefully applied, such as  
665 manufacturing process controls, sampling, traceability, and material diversion buffer at scale.

### *1. PQS Oversight*

666  
667 An effective PQS ensures that manufacturing changes, such as an increase in run time or other  
668 methods of scale-up, are appropriately evaluated by the facility's change management program.<sup>28</sup>  
669 Existing product and process understanding should be leveraged in evaluating change to  
670 determine the suitability of the change, adequacy of the control strategy, residual risks and  
671 associated mitigation strategy, and what type of new validation studies are necessary to plan and  
672 execute to support the change. These changes may be evaluated during an onsite inspection.

### *2. Postapproval Filing Strategies for Scale-Up*

673  
674 For an application product, one element of the change control is to determine an appropriate  
675 postapproval filing strategy based on the potential to impact the quality of the finished product  
676 and complexity of the change. A submission should include sufficient details on how the scale-  
677 up would be evaluated, including testing and sampling, acceptance criteria, and the number of  
678 runs supporting the change. Comparability protocols may also be useful for scale-up for  
679 application products (e.g., flow rate changes). As the complexity of the change may have a  
680 significant potential to impact the quality of the finished product, prior discussion with the  
681 Agency may be useful.<sup>29</sup>

682  
683 An increase in batch size by increasing only the run time with no changes to the approved  
684 manufacturing process, ranges, and equipment, is the most straightforward type of scale-up for  
685 continuous manufacturing processes, but still involves risks as noted above. Firms with a robust  
686 PQS and either experience with the subject product's continuous manufacturing process or  
687 experience with other suitably similar continuous manufacturing processes, may be able to  
688  
689  
690  
691

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<sup>28</sup> The elements of a robust change management program are described in guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006) and guidance for industry *ICH Q10 Pharmaceutical Quality* (April 2009).

<sup>29</sup> Refer to guidance for industry *Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization* (September 2016).

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692 manage the scale-up via an increase in the run time by the facility's PQS without a supplement  
693 or comparability protocol.

694

### **F. Stability**

696

697 Regulatory expectations for demonstrating adequate stability over the finished drug product's  
698 shelf life do not change between batch manufacturing and continuous processing. However, there  
699 are some differences that should be considered when developing the stability plan.

700

701 As described in guidance for industry *QIA(R2) Stability Testing of New Drug Substances and*  
702 *Products*, data from stability studies should be provided on at least three primary batches of the  
703 drug product, and where possible, these should be manufactured by using different batches of the  
704 drug substance. An applicant may take this approach when preparing a drug application using a  
705 continuous manufacturing process. Primary stability batches may be produced from shorter  
706 manufacturing runs, provided that a state of control is established and maintained when the  
707 process operates over the longer run times. Alternatively, stability samples could be obtained  
708 from a single continuous manufacturing campaign where manufacturing variability is captured  
709 (e.g., by introducing different batches of input material(s) in a sequential manner). If this latter  
710 approach is used, the stability samples should be collected to capture this variability.

711

### **G. Bridging Existing Batch to Continuous Manufacturing**

713

714 There may be situations where a continuous manufacturing process is proposed in a regulatory  
715 submission while a different process, such as a batch process, is used to make the clinical,  
716 bioequivalence, registration stability, or commercial batches. A company may also wish to  
717 introduce a continuous process at the later stage of development or as a postapproval  
718 manufacturing change.

719

720 A change from batch to continuous manufacturing is a change in the scientific operating  
721 principle, and it likely results in changes in many aspects of product and process design, such as  
722 equipment, process parameters, and control strategy. Therefore, the most appropriate filing  
723 strategy for a postapproval change to a continuous manufacturing process usually would be a  
724 prior approval supplement (PAS). A discussion with the Agency of the proposed change and the  
725 bridging strategy is encouraged to gain feedback prior to conducting the studies.<sup>30</sup>

726

727 An evaluation of the transition from batch to continuous manufacturing should include a  
728 comparison of individual unit operations, process parameters, equipment, CQAs, and the control  
729 strategy. In the cases where the continuous process may be based on the same unit operations  
730 and formulation as used for the batch process, the risk of change to product quality attributes  
731 (e.g., polymorphic form, dissolution, impurities, and stability) may be low and demonstration of  
732 in vitro equivalence may be sufficient to support such a change. Demonstration of in vitro  
733 equivalency may be supported by comparative batch data, including (not limited to)  
734 physicochemical properties (e.g., polymorphic form and particle size), impurity profiles, drug  
735 release profiles, and bridging stability data. However, there could be cases in which significant

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<sup>30</sup> See footnote 29.

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736 changes or novel approaches are used in switching from a batch to continuous manufacturing  
737 process. For example, the continuous process could incorporate a novel crystallization method  
738 that changes crystal form or a formulation change. These changes could pose a higher risk, and  
739 therefore may warrant additional in vivo bioequivalence studies. As these changes may impact  
740 safety, efficacy, and other aspects of an approved product, prior discussion with the Agency is  
741 recommended.<sup>31</sup>

742

### 743 **IV. LOCATION OF INFORMATION IN AN APPLICATION**

744

745 Information within submissions to FDA should be submitted in the Common Technical  
746 Document format in accordance with guidance for industry *M4Q: CTD – Quality*. Enhanced  
747 process development approaches should be provided as described in guidance for industry  
748 *Q8(R2) Pharmaceutical Development*. The table below provides recommendations for placement  
749 of information unique to continuous manufacturing (e.g., RTD) for drug product that may not be  
750 addressed in these documents.<sup>32</sup> The table is not a comprehensive list of the data requirements  
751 for a continuous manufacturing application; the application should contain all relevant  
752 information as required by 21 CFR part 314. Although not required, submission of an overview  
753 document to facilitate navigation may be helpful.

754

#### 755 **Recommendations for placement of information unique to continuous manufacturing**

756

<b>Information and Data</b>	<b>eCTD Location for Drug Products</b>
<b>Pharmaceutical Development</b>	
• Suitability of the proposed material attributes of raw materials, excipients, and drug substance for continuous feeding and manufacturability	3.2.P.2.1

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<sup>31</sup> See footnote 29.

<sup>32</sup> For the end-to-end continuous manufacturing process, the sponsor/applicant should consult with the Agency regarding the placement of information unique to this type of continuous manufacturing design prior to the NDA or ANDA submission.

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<b>Information and Data</b>	<b>eCTD Location for Drug Products</b>
<ul style="list-style-type: none"> <li>• Characterization of the process dynamics for the integrated system using a suitable scientific approach (e.g., RTD studies). Recommended information:               <ul style="list-style-type: none"> <li>▪ A description of the method or approach used to characterize the process dynamics</li> <li>▪ A science- and risk-based evaluation of the factors (material attributes, process parameters, equipment configuration) that may impact the process dynamics</li> </ul> <p>For RTD data: Representative RTDs reflecting routine commercial production conditions (e.g., grade of materials, mass flow rates, material transfer connections, and equipment). Characterization of the RTDs for mean residence time and shape of the distribution using a suitable measure, such as mean centered variance, standard deviation, or characteristic times (e.g., <math>t_{10}</math> and <math>t_{90}</math> or <math>t_5</math> and <math>t_{95}</math>).</p> </li> </ul>	3.2.P.2.3 3.2.P.4
<ul style="list-style-type: none"> <li>• Product and process characterization during normal operation and planned transient operations (e.g., start-up, shutdown)</li> </ul>	3.2.P.2.3
<ul style="list-style-type: none"> <li>• Material traceability strategy</li> <li>• Material collection and diversion strategy, including:               <ul style="list-style-type: none"> <li>▪ Justification for product collection</li> <li>▪ Potential events that trigger material diversion</li> <li>▪ The rationale for selection of the amount of material to be diverted (e.g., impacted material based on RTD and material traceability)</li> <li>▪ Description of the current criteria for rejection of the entire batch</li> </ul> </li> </ul>	3.2.P.2.3
<ul style="list-style-type: none"> <li>• Development data to support the proposed mass flow rate, run time, and process parameters and ranges.</li> </ul>	3.2.P.2.3
<ul style="list-style-type: none"> <li>• Supporting information for PAT and model development</li> <li>• Justification of finished product sampling strategies, including any backup methods when PAT device is unavailable</li> </ul>	3.2.P.2.3
<ul style="list-style-type: none"> <li>• Supporting information and rationale for advanced process control approaches (e.g., feedback, feedforward, model predictive), including identification of the controlled and manipulated parameters</li> </ul>	3.2.P.2.3
<b>Manufacture</b>	
<ul style="list-style-type: none"> <li>• Definition of batch size, including proposals for batch size ranges</li> </ul>	3.2.P.3.2

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<b>Information and Data</b>	<b>eCTD Location for Drug Products</b>
<ul style="list-style-type: none"> <li>• Process flow diagram with sufficient detail to describe continuous flow operational aspects. Elements which should be included are, among other things:                             <ul style="list-style-type: none"> <li>▪ Material flow including hold up steps and recycle loops</li> <li>▪ Rejection and/or diversion points</li> <li>▪ Critical process parameter ranges; design space (if applicable)</li> <li>▪ In-process controls, sampling and PAT locations</li> <li>▪ Advanced process controls used (e.g., feedback control)</li> </ul> </li> </ul>	3.2.P.3.3
<ul style="list-style-type: none"> <li>• Justification of sampling strategies for finished product testing, including any backup methods when PAT device is unavailable</li> <li>• Development and supporting data for PAT methods and models</li> </ul>	3.2.P.3.4
<ul style="list-style-type: none"> <li>• Description of advanced process control approaches (e.g., feedback, feedforward, model predictive)</li> </ul>	3.2.P.3.4
<b>Control of Drug Product</b>	
<ul style="list-style-type: none"> <li>• PAT methods used for release, including RTRT methods:                             <ul style="list-style-type: none"> <li>▪ Description of primary and alternate methods</li> <li>▪ Description of the statistical analysis of data</li> <li>▪ For submission of NIR based spectroscopic PAT methods, refer to guidance for industry <i>Development and Submission of Near Infrared Analytical Procedures</i></li> <li>▪ For submission of model based methods, refer to guidance for industry <i>Q8, Q9 &amp; Q10 Questions and Answers</i>   Appendix Q&amp;As from Training Sessions</li> </ul> </li> </ul>	3.2.P.5
<ul style="list-style-type: none"> <li>• Summary of the control overall strategy</li> </ul>	3.2.P.5.6

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## V. DEFINITIONS

761 **Active Process Control System:** A system consisting of hardware and software architecture,  
762 mechanisms, and algorithms that automatically adjusts a process to maintain the process output  
763 within a desired range.

764

765 **Automation System:** A broad range of systems to monitor and control the production of goods  
766 and services. The automated system can refer to computer hardware, software, peripheral  
767 devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals  
768 and standard operating procedures).<sup>33</sup>

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<sup>33</sup> Refer to International Society for Pharmaceutical Engineering’s Good Automated Manufacturing Practice Good Practices Guides and guidance for industry *Data Integrity and Compliance with CGMP* (December 2018).



## ***Contains Nonbinding Recommendations***

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770 **Batch:** A specific quantity of a drug or other material that is intended to have uniform character  
771 and quality, within specified limits and is produced according to a single manufacturing order  
772 during the same cycle of manufacture (21 CFR 210.3(b)(2)).  
773

774 **Continuous Manufacturing:** An integrated process that consists of a series of two or more unit  
775 operations (“the system”). In such a process, the input material(s) are continuously fed into and  
776 transformed within the process, and the processed output materials are continuously removed  
777 from the system.  
778

779 Although the amount of material being processed at any given instance may be relatively small  
780 in a continuous manufacturing process, the process can run over a period of time to generate  
781 necessary quantities of finished material with the desired quality in response to the market  
782 demand. There are different integration approaches for continuous pharmaceutical manufacturing  
783 processes. In an end-to-end approach, the drug substance and drug product process steps are fully  
784 integrated into a single continuous process and there is no isolated drug substance or  
785 intermediate. In a hybrid approach, a combination of batch and continuous process steps are used  
786 for drug substance or drug product manufacture.<sup>34</sup>  
787

788 **Control Strategy:** A planned set of controls, derived from current product and process  
789 understanding that assures process performance and product quality. The controls can include  
790 parameters and attributes related to drug substance and drug product materials and components,  
791 facility and equipment operating conditions, in-process controls, finished product specifications,  
792 and the associated methods and frequency of monitoring and control (*ICH Q10*).  
793

794 **Continued Process Verification:** Assurance that during routine production the process remains  
795 in a state of control.<sup>35</sup>  
796

797 **Disturbance:** A change to the input to the process (e.g., process parameter, material property,  
798 equipment condition, and/or environment) that is either intentionally or unintentionally  
799 introduced into the system.<sup>36</sup>  
800

801 **Lot:** A batch, or a specific identified portion of a batch, having uniform character and quality  
802 within specified limits; or, in the case of a drug product produced by continuous process, it is a  
803 specific identified amount produced in a unit of time or quantity in a manner that assures its  
804 having uniform character and quality within specified limits (21 CFR 210.3(b)(10)).  
805

806 **Pharmaceutical Quality System (PQS):** Management system to direct and control a  
807 pharmaceutical company with regards to quality (*ICH Q10*).  
808

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<sup>34</sup> In the hybrid approach, a drug manufacturer may implement continuous manufacturing for portions of a process, or for an entire process.

<sup>35</sup> See guidance for industry *Process Validation: General Principles and Practices* (January 2011).

<sup>36</sup> Adapted from Riggs JB (1999) *Chemical Process Control*, Lubbock, TX: Ferret Publishing.

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809 **Real Time Release Testing:** The ability to evaluate and ensure the quality of in-process and/or  
810 final product based on process data, which typically includes a valid combination of measured  
811 material attributes and process controls (*ICH Q8*).

812  
813 **Residence Time Distribution (RTD):** A probability distribution that describes the amount of  
814 time a mass or fluid element remains in a process.<sup>37</sup>

815  
816 **State of Control:** A condition in which the set of controls consistently provides assurance of  
817 continued process performance and product quality (*ICH Q10*).

818  
819 **Transient States:** Conditions where the process goes through dynamic period and a change  
820 happens over time. This change may be due to either disturbances or intentional alterations in the  
821 selected operating conditions.

822

## 823 VI. REFERENCES

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<sup>37</sup> Nasr, MM, et. al., *Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving From Theory to Practice*. September 26-27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals. J Pharm Sci. (Epub ahead of print).

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