

Q13 CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS

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FOREWORD

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed, registered, and maintained in the most resource-efficient manner. By harmonizing the regulatory expectations in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized safety reporting and marketing application submissions, and contributed to many other improvements in the quality of global drug development and manufacturing and the products available to patients.

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**INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE**

ICH HARMONISED GUIDELINE

**CONTINUOUS MANUFACTURING OF
DRUG SUBSTANCES AND DRUG PRODUCTS
Q13**

Draft version

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Q13
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ICH HARMONISED GUIDELINE
CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND
DRUG PRODUCTS

Q13

ICH Consensus Guideline

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1 **PART I: CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG**
2 **PRODUCTS**

3
4 **1. INTRODUCTION**

5 **1.1. Objective**

6 This guideline describes scientific and regulatory considerations for the development,
7 implementation, operation, and lifecycle management of continuous manufacturing (CM).
8 Building on existing ICH Quality guidelines, this guideline provides clarification on CM concepts
9 and describes scientific approaches and regulatory considerations specific to CM of drug
10 substances and drug products.

11 **1.2. Scope**

12 This guideline applies to CM of drug substances and drug products for chemical entities and
13 therapeutic proteins. It is applicable to CM for new products (e.g., new drugs, generic drugs,
14 biosimilars) and the conversion of batch manufacturing to CM for existing products. The principles
15 described in this guideline may also apply to other biological/biotechnological entities.

16
17 CM involves the continuous feeding of input materials into, the transformation of in-process
18 materials within, and the concomitant removal of output materials from a manufacturing process.
19 While this description may apply to an individual unit operation (e.g., tableting, perfusion
20 bioreactors), this guideline focuses on the integrated aspects of a CM system in which two or more
21 unit operations are directly connected. In this context, any changes made in a unit operation of CM
22 may have a direct and often immediate impact on downstream and upstream (e.g., via a feedback
23 control) unit operations.

24
25 Fundamental aspects of CM that are generally not specific to technology, dosage form, or molecule
26 type are described within the main body of this guideline. Annexes are provided to augment the
27 main guideline by providing illustrative examples and considerations specific to certain modalities
28 (e.g., chemical entities, therapeutic proteins), technologies, and production methods (e.g.,
29 integration of drug substance and drug product manufacturing). The examples and approaches
30 described in these annexes are not exhaustive, and alternative approaches can be used. Topics that
31 are broadly applicable to both CM and batch manufacturing are not in the scope of this guideline,
32 and other existing ICH guidelines should be used as appropriate.

33 **2. CM CONCEPTS**

34 **2.1. Different Modes of CM**

35 CM can be applied to some or all unit operations in a manufacturing process. Examples of CM
36 modes include:

- 37
38
- 39 • A combination of manufacturing approaches in which some unit operations operate in a
40 batch mode while others are integrated and operate in a continuous mode
 - 41 • A manufacturing approach in which all unit operations of a drug substance or drug product
42 manufacturing process are integrated and operate in a continuous mode

- 43
- 44 • A manufacturing approach in which drug substance and drug product unit operations are
- 45 integrated across the boundary between drug substance and drug product to form a single
- 46 CM process (i.e., the drug substance is continuously formed and processed through
- 47 integrated unit operations to result in the final drug product)
- 48

49 A manufacturing approach may incorporate surge lines or tanks to maintain a constant flow of

50 material inputs and outputs in any mode of CM described above.

51 **2.2. Batch definition**

52 The ICH Q7 definition of a batch is applicable to all modes of CM, for both drug substances and

53 drug products. Based on this definition, the size of a batch produced by CM can be defined in

54 terms of one of the following:

55

- 56 • Quantity of output material
- 57 • Quantity of input material
- 58 • Run time at a defined mass flow rate
- 59

60 Other approaches to define batch size can also be considered, if scientifically justified based on

61 the characteristics of the CM process.

62

63 A batch size can also be defined as a range. For example, a batch size range can be established by

64 defining a minimum and maximum run time.

65 **3. SCIENTIFIC APPROACHES**

66 **3.1. Control Strategy**

67 The development of a successful control strategy for CM is enabled by a holistic approach,

68 considering aspects specific to CM (discussed below) and the principles described in ICH Q7–

69 Q11.

70 **3.1.1. State of Control**

71 A state of control (ICH Q10) is a condition that provides assurance of continued process

72 performance and product quality. The condition may vary, depending on the mode of CM and the

73 specific process steps. For example, a state of control can be demonstrated for some CM processes

74 when a set of parameters (e.g., process parameters, quality attributes) are within specified ranges,

75 but the processes are not necessarily in a steady state condition. Elements of the control strategy

76 monitor a state of control and, when necessary, take appropriate actions to maintain control of the

77 process. It is important to have mechanisms in place to evaluate the consistency of operation and

78 to identify situations in which parameters are within the specified range yet outside historical

79 operating ranges, or they are showing drifts or trends. The latter situation may indicate that the

80 process is at risk of operating outside the specified operating range and warrants evaluation and,

81 when necessary, corrective action.

82 **3.1.2. Process Dynamics**

83 Knowledge of process dynamics is important to maintaining state of control in CM. Specifically,

84 understanding how transient events propagate helps to identify risks to product quality and to

85 develop an appropriate control strategy (see Section 3.1.5 for process monitoring and control
86 considerations). Transient events that occur during CM operation may be planned (e.g., process
87 start-up, shutdown and pause) or unplanned (e.g., disturbances).
88

89 Characterisation of the residence time distribution (RTD) can be used to help understand process
90 dynamics. RTD characterises the time available for material transport and transformation, and it
91 is specific to the process, composition/formulation, material properties, equipment design and
92 configuration, etc. Understanding process dynamics (e.g., through the RTD) enables the tracking
93 of material and supports the development of sampling and diversion strategies, where applicable.
94 In addition, such understanding is of importance from a process performance perspective. For
95 example, process dynamics may impact process characteristics, such as selectivity in the
96 manufacture of chemical entity drug substances and viral safety in the manufacture of therapeutic
97 protein drug substances.
98

99 Process dynamics should be characterised over the planned operating ranges and anticipated input
100 material variability using scientifically justified approaches. Appropriate methodologies (e.g.,
101 RTD studies, in silico modeling with experimental confirmation) should be used to understand the
102 impact of process dynamics and its variation on material transport and transformation. These
103 methodologies should not interfere with the process dynamics of the system, and the
104 characterisation should be relevant to the commercial process. For example, when conducting
105 RTD studies, the tracer used to replace a constituent of the solid or liquid stream should have
106 highly similar flow properties as those of the constituent replaced. A tracer should also be inert to
107 the other components of the process and should not alter how processed materials interact with
108 equipment surfaces. Step testing by making small changes to the quantitative composition of the
109 process stream (e.g., small increments of a constituent) is another useful technique to determine
110 the RTD and avoid the addition of an external tracer to the process. Other approaches can be used;
111 the approach taken should be justified.

112 **3.1.3. *Material Characterisation and Control***

113 Material attributes can impact various aspects of CM operation and performance, such as material
114 feeding, process dynamics, and output material quality. Understanding the impact of material
115 attributes and their variability on process performance and product quality is important for the
116 development of the control strategy. Input materials may require evaluation and control of
117 attributes beyond those typically considered for a material specification used in batch
118 manufacturing. For example:
119

- 120 • For a solid dosage form process, particle size, cohesiveness, hygroscopicity, or specific
121 surface area of drug substances and excipients may impact the feeding of powders and
122 material flow through the system.
123
- 124 • For a chemically synthesised drug substance process, viscosity, concentration, or the
125 multiphase nature (e.g., presence of solids) of the feeding solution may impact flow
126 properties or conversion.
127
- 128 • For a therapeutic protein (e.g., monoclonal antibodies) process, the higher variability of
129 feed stocks such as metal salts, vitamins, and other trace components may adversely impact

130 cell culture performance. Prolonged run times may require different lots of media, buffers,
131 or other starting materials for the downstream CM process, potentially introducing more
132 variabilities to the process.

133 **3.1.4. Equipment Design and System Integration**

134 The design of equipment and their integration to form a CM system impacts process dynamics,
135 material transport and transformation, output material quality, etc. When developing a CM process
136 and its control strategy, it is important to consider the characteristics of individual equipment as
137 well as those of the integrated system that can affect process performance. These include the
138 system's ability to maintain a continuous flow of input and output materials, manage potential
139 disruption to CM operations (e.g., filter changes), and complete the intended transformation of the
140 material stream within the respective planned operational ranges of the equipment. Examples of
141 design considerations are given below:

- 142
- 143 • Design and configuration of equipment (e.g., compatibility and integrity of equipment
144 components for the maximum run time or cycles; geometry of constituent parts to promote
145 the desired transformation; spatial arrangement of equipment to facilitate material flow and
146 avoid build-up or fouling)
- 147
- 148 • Connections between equipment (e.g., use of a surge tank between two unit operations to
149 mitigate differences in mass flow rates)
- 150
- 151 • Locations of material diversion and sampling points (e.g., selection of locations for a
152 diverter valve and sampling probe without interrupting material flow and transformation)
- 153

154 Furthermore, appropriate design or selection of equipment for a CM process may enable process
155 simplification, facilitate process monitoring and material diversion, and improve process
156 capability and performance. For example, in a drug substance process, reactor design can
157 effectively reduce formation and build-up of impurities, resulting in fewer purification steps.
158 Similarly, for therapeutic protein drug substance manufacturing, system design can enable process
159 intensification and reduce cycle times.

160 **3.1.5. Process Monitoring and Control**

161 Process monitoring and control support the maintenance of a state of control during production
162 and allow real-time evaluation of system performance. Common approaches to process monitoring
163 and control—including establishment of target setpoints and control limits, design space, and
164 specifications for attributes being measured—are applicable to CM.

165

166 Process analytical technology (PAT) (ICH Q8) is well-suited for CM. Example applications
167 include in-line UV flow cells to monitor therapeutic protein concentration information, in-line
168 near-infrared spectroscopy to assess blend uniformity, and in-line particle size analysis to monitor
169 the output of a crystalliser. The use of PAT enables disturbances to be detected in real time.
170 Therefore, CM is readily amenable to automated process control strategies based on, for example,
171 active control such as feedforward or feedback control. Principles of control strategy as described
172 in ICH Q8 and ICH Q11 can be applied to CM processes.

173

174 An appropriate sampling strategy is an important aspect of process monitoring and control. The
175 variables monitored, monitoring method and frequency, amount of material sampled (either
176 physical sampling or data sampling using in-line measurement), sampling location, statistical
177 method, and acceptance criteria depend on the intended use of the data (e.g., detection of rapid
178 changes such as disturbances, assessment of quality of a batch when real-time release testing
179 (RTRT) (ICH Q8) is used, analysis of process trends or drifts) and process dynamics. Another
180 important consideration is the avoidance of measurement interference with the process.
181 Assessment of risks associated with data gaps (e.g., PAT recalibration, refill of a feeding system,
182 failure of system components) should inform whether contingency methods are required.

183 **3.1.6. Material Traceability and Diversion**

184 CM processes may include periods when non-conforming materials are produced, for example,
185 during system start-up and shutdown and when disturbances are not appropriately managed and
186 mitigated. The ability to divert potential non-conforming material from the product stream during
187 production is an important characteristic of CM and should be considered in developing the control
188 strategy.

189
190 Understanding the process dynamics of individual unit operations and integrated systems over
191 planned operating conditions enables tracking of the distribution of materials over time. This
192 allows input materials to be traced throughout production. Material traceability, understanding
193 how upstream disturbances affect downstream material quality, and the use of appropriate
194 measurements (e.g., PAT) allow for real-time determination of when to start and stop material
195 collection or diversion. The amount of material diverted can be influenced by several factors, such
196 as process dynamics, control strategy, severity (e.g., magnitude, duration, frequency) of the
197 disturbances, and location of the sampling and diversion points. Additionally, it is important that
198 the diversion strategy accounts for the impact on material flow and process dynamics when
199 material is diverted. Criteria should be established to trigger the start and end of the diversion
200 period and restart of product collection.

201 **3.1.7. Process Models**

202 Process models can be used for development of a CM process or as part of a control strategy for
203 commercial production, including the diversion strategy. Process models may also be used to
204 predict quality attributes in real time, enabling timely process adjustments to maintain a state of
205 control. During development, process models can support the establishment of a design space by
206 explaining how inputs (e.g., process parameters, material attributes) and outputs (e.g., product
207 quality attributes) are related. Through use of *in silico* experimentation, process models also
208 enhance process understanding and can reduce the number of experimental studies.

209
210 For general considerations regarding models (including implications of model impact to validation
211 requirements), refer to *Points to Consider: ICH-Endorsed Guide for ICH Q8/Q9/Q10*
212 *Implementation*.¹ For CM applications, additional considerations are discussed below.

- 213
214 • A process model is specific to system design and configuration and relevant material
215 properties.

¹ This FDA guidance for industry is published as Q8, Q9, & Q10 Questions and Answers -- Appendix: Q&As from Training Sessions (Q8, Q9, & Q10 Points to Consider) (August 2012).

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- Model development requires an understanding of the underlying model assumptions (e.g., plug flow versus mixed flow systems) and when these assumptions remain valid. Risk assessments, sound scientific rationales, and relevant data inform the selection of model inputs and model-governing equations. It is important to determine the relevant inputs that affect the model performance, based on appropriate approaches such as sensitivity analysis.
- Model performance depends on factors such as mathematical constructs and the quality of model inputs (e.g., noise, variability of data). When setting acceptance criteria for model performance, the model's intended use and the statistical approaches that account for uncertainty in the experimental measurement and model prediction should be considered.
- Model validation assesses the fitness of the model for its intended use based on predetermined acceptance criteria. Model validation activities are primarily concerned with demonstrating the appropriateness of the underlying model assumptions and the degree to which sensitivity and uncertainty of the model and the reference methods are understood.
- Monitoring of model performance should occur on a routine ongoing basis and when a process change (e.g., input material, process parameter change) is implemented. A risk-based approach to assess the impact of a model change (e.g., optimisation of model performance, change of the model's intended use, change of underlying model assumptions), scope of model development, and model validation criteria enables effective and efficient lifecycle management of models. Depending on the extent of a change and its impact on model performance, a model may need to be redeveloped and validated.

240 3.2. Changes in Production Output

241 Several considerations associated with some common approaches to production changes are
242 discussed below, and variations to these approaches are also possible. For already approved
243 products, it is important to justify the selected approach, understand its impact on the overall
244 control strategy and process performance, and, as needed, update the control strategy. Some
245 changes may require process modification and process validation.

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- **Change in run time with no change to mass flow rates and equipment:** Issues not observed over shorter run times may become visible as run time increases. Additional risks and constraints should be considered and may include, for example, process drift, increased heat, material build-up, exceeding the performance limit of components (e.g., validated *in vitro* cell age, resin cycle number, measurement system calibration status), material degradation, membrane or sensor fouling, and microbial contamination. Decreasing production output (below the longest run time previously validated) should not imply additional risks, given the same equipment, process and control strategy are used.
- **Increase mass flow rates with no change to overall run time and equipment:** The risks associated with this approach may impact output material quality and are related to changes in process dynamics and system capability to handle increased mass flow rates. Therefore, this approach may require re-evaluation and modification of the control strategy, including

260 process parameters and controls, material traceability, RTD, sampling, and diversion
261 strategies.

- 262
- 263 • **Increase output through duplication of equipment (i.e., scale-out):** Considerations for
264 two commonly used scale-out approaches are provided below.
265
 - 266 ○ *Replication of production lines (like-for-like):* Replicating the integrated CM
267 production line (i.e., same equipment and setup as the original CM system) can be
268 used to increase production output. The replicate production lines follow the same
269 control strategy.
270
 - 271 ○ *Parallel unit operations on the same production line:* When only some unit
272 operations are replicated on the same line, risks are associated with maintaining
273 control across parallel unit operations. Aspects to consider are maintenance of
274 uniform flow distribution among the parallel operations, re-integration of parallel
275 flow streams, changes to process dynamics, and material traceability.
276
 - 277 • **Scale up by increasing equipment size/capacity:** Depending on the process and
278 equipment design, increasing production by increasing equipment size may be possible.
279 General principles of equipment scale-up as in the case of batch manufacturing apply. As
280 elements such as RTD, process dynamics, and system integration may change, various
281 aspects of the control strategy may be impacted. The applicability of the original control
282 strategy should be assessed at each scale and modified where needed.

283 3.3. Continuous Process Verification

284 In CM, frequent process monitoring and control can be achieved through use of PAT tools, such
285 as in-line/online/at-line monitoring and control, soft sensors and models. These tools allow real-
286 time data collection for parameters relevant to process dynamics and material quality, and hence
287 ensure the state of control for every batch. Additionally, since CM can facilitate changes to
288 production output without increasing equipment size, there is an opportunity to generate
289 development knowledge at the same scale intended for commercial manufacturing. These tools,
290 together with the system design and the control strategy, facilitate early execution of process
291 validation activities and the adoption of continuous process verification (ICH Q8) as an alternative
292 to traditional process validation.

293 4. REGULATORY CONSIDERATIONS

294 4.1. Process Description

295 In line with ICH M4Q, a sequential narrative description of the manufacturing process should be
296 included in sections 3.2.S.2.2 and 3.2.P.3.3 of the Common Technical Document (CTD) and
297 supported by pharmaceutical development data provided in CTD sections 3.2.S.2.6 or 3.2.P.2.3.
298 In the case of CM, the process description should be supplemented by:

- 300 • A description of the CM operational strategy indicating the operating conditions (e.g., mass
301 flow rates, setpoints, ranges), in-process controls or tests, criteria that should be met for

- 302 product collection during routine manufacturing, and strategy for material collection and,
303 when applicable, diversion
304
- 305 • When appropriate, a description of how the material is transported from one piece of
306 equipment to another (e.g., vertical, horizontal or pneumatic conveying system)
307
 - 308 • A flow diagram outlining the direction of material movement through each process step,
309 with the following aspects identified, when applicable:
310
 - 311 ○ Locations where materials enter and leave the process (including material diversion
312 and collection points)
 - 313
 - 314 ○ Locations of unit operations and surge lines or tanks
 - 315
 - 316 ○ Clear indication of the continuous and batch process steps
 - 317
 - 318 ○ Critical steps and points at which process monitoring and controls (e.g., PAT
319 measurement, feedforward or feedback control), intermediate tests, or final product
320 controls are conducted
 - 321
 - 322 • A suitably detailed description of any aspects of equipment design or configuration and
323 system integration that were shown during development to be critical to process control or
324 to impact product quality

325 4.2. Control Strategy

326 The control strategy of a CM process is designed to ensure that output materials made over the run
327 time are of the desired quality. The control strategy should consider the elements discussed in
328 Section 3 of this guideline. It should describe the relevant controls and approaches used during
329 manufacturing and the operational aspects of the CM process. Some aspects of the control strategy
330 are discussed below.

- 331
- 332 • **Input material attributes:** Impact of input material attributes and their variability (e.g.,
333 intra-batch, inter-batch, different suppliers) on continuous processing should be assessed
334 and proposed material attribute acceptable ranges should be justified when establishing the
335 material specification. For input materials for which pharmacopoeial requirements exist,
336 characterisation and control may extend beyond those requirements.
337
- 338 • **Process monitoring and control:** An appropriate description should be provided in the
339 dossier to show a robust approach to monitoring and maintaining a state of control.
340 Approaches on how the control system uses process parameters and in-process material
341 attribute measurements to make process- and quality-related decisions (e.g., to pause the
342 process or divert material) should be described. Other important aspects should be defined,
343 such as the sampling strategy (e.g., location, sample size, frequency, statistical approach
344 and criteria, and their relevance to the intended use), summary of the models if used (e.g.,

345 multivariate statistical process control), and the use of data in making in-process control
346 decisions (e.g., to trigger material diversion). Fluctuations or variability that may occur
347 during the CM process should not be masked by the data analysis method used. For
348 example, when data averaging is used, averaging across appropriate time-based intervals
349 should be considered rather than data averaging across the time for an entire CM run.
350 Therefore, statistical sampling plans and data analysis should be described and justified.

- 351
- 352 • **System operation:** Procedures should be established and maintained on site for managing
353 system start-up, shutdown, and pauses and for handling disturbances (see Annex V).
354 Relevant approaches for these operations (e.g., handling disturbances) should be described
355 at an adequate level of detail in the dossier. The disposition of material impacted by
356 transient and pause events should be justified, considering potential risks to output material
357 quality (e.g., the impact of a disturbance as it propagates downstream).
358
 - 359 • **Material diversion and collection:** The material diversion and collection strategy should
360 be described and justified. The strategy described should include the criteria for triggering
361 material diversion, the basis for determining the amount of diverted materials, the
362 conditions for resuming material collection, etc. Factors such as sampling frequency, RTD,
363 and amplitude, duration and propagation of disturbances should be considered in
364 developing the diversion strategy. The amount of diverted material should appropriately
365 incorporate justified safety margins, considering the uncertainty of RTD and other
366 measurements. Procedures for managing material collection, diversion, and disposition
367 (e.g., quarantine, offline testing, investigations) do not need to be included in the dossier
368 but should be maintained within the pharmaceutical quality system (PQS) (ICH Q10).
369
 - 370 • **RTRT:** RTRT may be applied to some or all of the output material quality attributes. RTRT
371 is not a regulatory requirement for CM implementation. When RTRT is proposed, the
372 associated reference test method should be described. Development of the data collection
373 approach for RTRT implementation should include a risk assessment of how any lapses in
374 data collection (e.g., recalibrating a near infrared (NIR) probe) may affect decisions
375 relating to product quality. The proposed control strategy should include alternative or
376 additional quality controls to mitigate the risks to product quality posed by these scenarios.
377 If the results from RTRT fail or are trending towards failure, appropriate investigations
378 should be conducted. Refer to *Points to Consider: ICH-Endorsed Guide for ICH*
379 *Q8/Q9/Q10 Implementation* for discussion of models used as surrogates for traditional
380 release testing methods.²
381
 - 382 • **Equipment and system integration:** Aspects of equipment design and system integration
383 that are shown to be critical to output material quality and its control should be described
384 and justified in the context of the overall control strategy.
385

386 A summary of the control strategy should be provided in CTD section 3.2.S.2.6 or 3.2.P.2.3 with
387 links to the CTD sections that contain the detailed information to enable the understanding and
388 evaluation of the manufacturing process and how it is controlled.

² Ibid

389 4.3. Batch Description

390 The approach to define batch size (see examples in Section 2.2) and the proposed commercial
391 batch size or range should be described in the dossier.

392
393 If a range is proposed, it should be justified, and the approach for achieving the range should be
394 described (Section 2.2). Changes in batch size within the proposed batch size range can be
395 managed within the PQS. Any post-approval change to the production output beyond the approved
396 range should be supported by data (Section 3.2) and appropriately managed (i.e., prior approval or
397 notification).

398
399 A suitable quantitative metric should be defined to establish batch-to-batch consistency and system
400 robustness. For example, when a batch size is defined by the amount of collected material, the
401 amount of diverted materials relative to that of collected materials for each batch should be
402 considered.

403
404 The actual intended size of a given batch should be defined before manufacturing begins and
405 should be managed under the PQS.

406 4.4. Process Models

407 The scope of model development, validation, and maintenance and the details provided in the
408 dossier should be commensurate with the model type and impact category. The process model
409 should be specific for the defined system (e.g., equipment, layout, connections). All information
410 for models used as part of commercial manufacturing should be maintained at the manufacturing
411 site. Refer to *Points to Consider: ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation* for
412 regulatory expectations on process models.³

413 4.5. Drug Substance and Drug Product Stability

414 Regulatory expectations for the stability data package generally do not differ between CM and
415 batch manufacturing (see, e.g., ICH Q1A, ICH Q5C). The concept of using a pilot scale batch
416 (e.g., at a minimum, one-tenth of a full production scale) for stability studies, as defined in other
417 guidelines (e.g., ICH Q1A), may not be applicable to CM. See Section 3.2 for considerations that
418 should be taken into account if production output between stability and commercial batches is
419 different.

420
421 Batches used to generate primary stability data should be manufactured using a manufacturing
422 process and equipment representative of the commercial process. Primary stability batches should
423 incorporate the variability described in the ICH stability guidelines (e.g., different drug substance
424 batches or different cell bank vials). Multiple stability batches may be produced from shorter
425 manufacturing runs at the same mass flow rate, provided it is demonstrated that a state of control
426 is established and maintained when the process operates over the longer commercial run times.
427 Alternatively, for chemical entities, a single CM run with a single start-up/shutdown sequence
428 could be used to obtain the stability batches when the aforementioned variability is incorporated
429 into the batches (e.g., by introducing different batches of drug substances in a sequential manner).

³ Ibid

430 4.6. Conversion of a Batch Process to CM

431 Changing the manufacturing mode from batch to continuous necessitates the development of an
432 appropriate control strategy, considering factors identified in Section 3. The output materials from
433 the batch and continuous processes should have comparable quality. A science and risk-based
434 approach should be used for establishing product comparability and assessing the need for
435 additional bioequivalence, non-clinical or clinical studies, and stability data. Additional details
436 regarding how to establish product comparability for therapeutic proteins can be found in ICH
437 Q5E. Manufacturers should seek regulatory approval before the conversion of an approved batch
438 process to a CM process. Manufacturers can seek advice from the regulatory authority to gain
439 clarification on the regulatory expectations and acceptability of their strategy and data package for
440 the proposed changes (e.g., potential changes in formulation required to enable conversion to CM
441 and the impact of these changes on product registration).

442 4.7. Process Validation

443 The requirements for process validation as established by region are similar for CM and batch
444 manufacturing processes. In addition to a traditional process validation approach that uses a fixed
445 number of validation batches, a continuous process verification approach may be used. The use of
446 a continuous process verification approach should be justified based on the product and process
447 understanding, system design, and overall control strategy.

448
449 When continuous process verification is used, the CM system performance and material quality
450 should be continuously monitored, such that the real-time data collected demonstrate the
451 maintenance of a state of control and production of output material with the desired quality for the
452 run time duration. The dossier should contain justifications to support the adequacy of a proposed
453 control strategy for continuous process verification.

454
455 When a continuous process verification approach is used to support initial product launch,
456 applicants should define when validation activities are considered sufficient to provide confidence
457 in the commercial manufacturing process.

458 4.8. Pharmaceutical Quality System

459 PQS expectations are the same for batch and CM processes and should follow pertinent ICH
460 guidelines. One important operational aspect of CM is that non-conforming materials can be
461 diverted from the rest of the batch when material traceability, process monitoring, and material
462 diversion strategies are well established. Procedures for material diversion, when required, should
463 be established under the PQS (see Section 4.2). Diverted materials resulting from planned events
464 (e.g., system start-up and shutdown) generally do not require investigation when the events meet
465 established process performance criteria. Examples of approaches for managing disturbances are
466 provided in Annex V. As described therein, when unexpected disturbances occur, appropriate
467 investigation, root cause analysis, and corrective action and preventive action (CAPA) should be
468 instituted. An overarching plan or decision tree that describes how disturbances are managed for
469 various categories of material diversion should be maintained under the PQS.

470

471 **4.9. Lifecycle Management**

472 The principles and approaches described in ICH Q12 are applicable to the lifecycle management
 473 of CM. Additional lifecycle management aspects related to conversion of a batch to a CM process
 474 for existing products can be found in Section 4.6.

475 **4.10. Submission of CM-Specific Information in the CTD**

476 The dossier should include information as outlined in ICH M4Q. Additional elements relevant to
 477 CM should also be provided in the dossier when applicable; some of these elements are listed in
 478 Table 1. In the case of integrated drug substance and drug product CM processes, some information
 479 and data, such as an integrated flow diagram, may be presented in CTD section 3.2.P with a cross
 480 reference in 3.2.S (see Annex IV for additional details).

481 **Table 1: CM-specific information in the CTD**

CTD section	Information and Data
<p>3.2.S.2.6 3.2.P.2.3</p>	<p>Manufacturing Process Development</p> <ul style="list-style-type: none"> • Summary of the overall process development, including all relevant control strategy elements (with links to the CTD sections that contain detailed information), for example: <ul style="list-style-type: none"> ○ Description and justification of the system start-up, shutdown and pauses ○ Description and justification of the material diversion and collection strategy ○ Description of feedforward and feedback controls • Development and justification of process models, if used • Summary of disturbance management
<p>3.2.S.2.2 3.2.P.3.2</p>	<p>Batch Definition</p> <ul style="list-style-type: none"> • Batch size or range, and approach to achieving the intended batch size or range
<p>3.2.S.2.2 3.2.P.3.3</p>	<p>Description of Manufacturing Process and Process Controls</p> <ul style="list-style-type: none"> • Commercial manufacturing process description, including flow diagram and equipment scheme • Process controls and limits (e.g., input rates/mass flow rates, feeder control limits) • Critical process parameters • Active controls (e.g., feedforward or feedback control) and process models, if these elements are part of the control strategy • Criteria for product collection, including control limits and strategy for segregation and diversion to waste • Description of equipment and system integration critical to the output material quality • Overview of high-impact process models, if used

3.2.S.2.4 3.2.P.3.4	Controls of Critical Steps and Intermediates <ul style="list-style-type: none"> • Summary of in-process testing or control and acceptance criteria • Sampling plan for in-process testing or control • High-impact process model validation data and maintenance protocol, if used
3.2.S.4.1/4.2 3.2.P.5.1/5.2	Specification / Analytical Procedures <ul style="list-style-type: none"> • Description of the RTRT methods and criteria, where used for release
3.2.S.4.5 3.2.P.5.6	Justification of Specifications <ul style="list-style-type: none"> • Summary of the analytical control strategy (including alternative plans instituted when potential gaps in PAT data occur, where relevant) • Justification of the overall control strategy with links to the detailed information in appropriate CTD sections (if it is not included in section 3.2.S.2.6 or 3.2.P.2.3)
3.2.R	Regional Information <ul style="list-style-type: none"> • Applicable information in accordance with ICH M4Q (e.g., continuous process verification scheme, executed batch records)

483 **5. GLOSSARY**484 **Active Controls:**

485 A system consisting of hardware and software architecture, mechanisms, and algorithms
486 that automatically adjust a process to maintain the process output within a desired range.
487 Examples include feedforward and feedback controls.

488

489 **Batch (or Lot):**

490 A specific quantity of material produced in a process or series of processes that is expected
491 to be homogeneous within specified limits. In the case of continuous production, a batch
492 may correspond to a defined fraction of the production. The batch size can be defined either
493 by a fixed quantity or by the amount produced in a fixed time interval.

494

495 **Disturbances:**

496 Unplanned changes to process inputs beyond normal operating range or conditions (e.g.,
497 process parameter, material property, equipment condition, or environment) that are
498 introduced into a system.

499

500 **Diversion:**

501 Procedure in which materials are isolated and separated from the product stream in the
502 manufacturing process.

503

504 **Material Traceability:**

505 The ability to track the distribution of materials throughout the manufacturing process.

506

507 **Model Maintenance:**

508 A set of planned activities over the product lifecycle to monitor and sustain the model's
509 performance to continually ensure its suitability for the intended and approved purpose.

510

511 **Multivariate Statistical Process Control:**

512 The application of multivariate statistical techniques to analyse complex process data with
513 potentially correlated variables. (EP)

514

515 **Process Dynamics:**

516 The response of a manufacturing process to changing conditions or transient events.

517

518 **Residence Time Distribution (RTD):**

519 A measure of the range of residence times experienced by material passing through a
520 specific process environment/vessel/unit operation. (ASTM E2968-14)

521

522 **Run Time:**

523 The time interval used to produce a quantity of output material.

524

525 **Soft Sensors:**

526 A model that is used in lieu of physical measurement to estimate a variable or attribute
527 (e.g., a quality attribute of material) based on measured data (e.g., process data). The model
528 development, including selection of such data variables, is driven by comprehensive
529 product and process understanding.

530

531 **Steady State:**

532 A stable condition that does not change over time.

533

534 **System:**

535 A manufacturing architecture that, in the context of CM, consists of individual pieces of
536 equipment, their connections to one another and to monitoring and control systems, and
537 spatial layout.

538

539 **Transient Events:**

540 A temporary condition in which a process goes through a dynamic change. This change
541 may be due to a disturbance or an intentional alteration in the selected operating conditions
542 (e.g., start-up, shutdown, changes from one operating condition to another).

543

544 **Unit Operation:**

545 A basic step in a process. Unit operations involve a physical or chemical transformation
546 such as a reaction, crystallisation, blending, purification, granulation, filtration, and virus
547 inactivation.

548

549 **6. REFERENCES**

- 550 ASTM E2968-14: Standard Guide for Application of Continuous Processing in the Pharmaceutical
551 Industry
552
553 European Pharmacopoeia (EP)
554
555 ICH Q1A: Stability Testing of New Drug Substances and Products
556
557 ICH Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological
558 Products
559
560 ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their
561 Manufacturing Process
562
563 ICH Q6A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and
564 New Drug Products: Chemical Substances
565
566 ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
567
568 ICH Q8: Pharmaceutical Development
569
570 ICH Q9: Quality Risk Management
571
572 ICH Q10: Pharmaceutical Quality System
573
574 ICH Q11: Development and Manufacture of Drug Substances (Chemical Entities and
575 Biotechnological/Biological Entities)
576
577 ICH Q12: Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle
578 Management
579
580 ICH M4Q: The Common Technical Document for The Registration of Pharmaceuticals for Human
581 Use: Quality
582
583 Points to Consider: ICH-Endorsed Guide for ICH Q8/Q9/Q10 Implementation

584 **PART II: ANNEXES**

585

586 **ANNEX I: CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES FOR**
 587 **CHEMICAL ENTITIES**

588

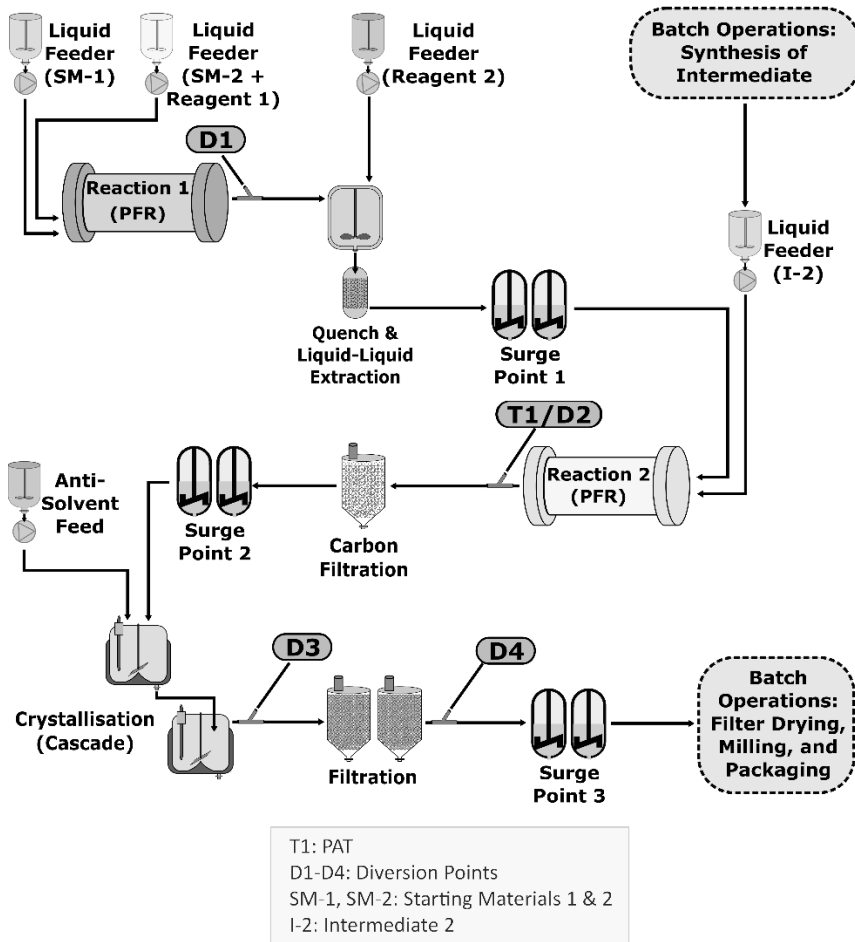
589 **1. INTRODUCTION AND EXAMPLE SYSTEM OVERVIEW**

590 This annex exemplifies one approach to implement CM of drug substances for chemical entities
 591 based on the scientific principles described in the main guideline. The discussion points presented
 592 here are not exhaustive for drug substance CM systems. Alternative approaches can be used.
 593

594 Figure 1 illustrates a drug substance manufacturing process containing both continuous and batch
 595 operations. It is not intended to represent a regulatory flow diagram. The continuous process
 596 segment consists of unit operations that can be characterised as having two plug-flow reactors
 597 (PFRs), liquid phase extraction, carbon filtration, continuous crystallisation, and filtration.
 598 Manufacture of Intermediate 2 is performed in batch mode, as is final processing including filter
 599 drying, milling, and packaging. This annex focuses on the continuous elements of this process.
 600

601

602 **Figure 1: Example of a drug substance CM system for chemical entities**



603

604 2. CONTROL STRATEGY AND OTHER TECHNICAL CONSIDERATIONS

605 The CM system and its control strategy were designed to control parameters that impact the
606 manufacture and quality of the drug substance, including impurity profile and physicochemical
607 properties. The overall control strategy was developed in accordance with the main guideline and
608 ICH Q7–Q11.

609 2.1. Equipment Design and Integration

610 Within the continuous process segment in Figure 1 (Section 1 of this annex), the following
611 processes occur:

- 612
613 • Reaction 1: Starting materials 1 and 2 are coupled in a PFR to produce Intermediate 1.
614 Diversion Point D1 is located after the PFR to permit material diversion when PFR
615 conditions are outside predefined acceptance criteria. The reaction is quenched as an
616 integrated operation after the PFR, and unwanted by-products are removed by liquid-liquid
617 extraction. The resultant solution (Intermediate 1) is used as an input for the second
618 reaction without isolation.
- 619
620 • Reaction 2: Intermediate 1 and Intermediate 2 (prepared upstream through separate batch
621 unit operations) are coupled in a second PFR to form the crude drug substance. The online
622 PAT near the reactor exit (T1) monitors conversion of Intermediate 1 to the crude drug
623 substance. Diversion Point D2 located after PAT is used to divert non-conforming material.
624
- 625 • Drug Substance Isolation: The crude drug substance is purified by carbon filtration and
626 continuous two-stage crystallisation. The crystal slurry is filtered by using two identical
627 filtration units running in an alternating fashion. This setup enables continuous processing
628 of the drug substance after crystallisation by allowing the collection of crystallised products
629 on one filter unit at the same time product isolated on the second filter is discharged.
630 Diversion Points D3 and D4 allow for material diversion at the crystalliser and just before
631 batch operations, respectively. A batch dry milling operation is used to achieve the desired
632 particle size distribution of the crystallised drug substance.

633
634 Three surge points (each containing multiple surge tanks) are used: one before Reaction 2, another
635 before the two-stage continuous crystallisation, and one just before final batch operations. These
636 are important components of the system design and control strategy, as they improve process
637 robustness and mitigate temporary differences in mass flow rates by decoupling upstream and
638 downstream operations.

639
640 The design of the overall system and each unit operation, along with the control strategy, optimise
641 material quality. For example, PFR design elements (i.e., dimension and configuration) allow
642 precise control of temperature, mixing, and reactant flows. These parameters were shown during
643 development to be important to the drug substance impurity profile.

644 2.2. Process Control and Monitoring

645 Holistic controls used across Reactions 1 and 2 ensure consistent operations and quality of the
646 resulting crude drug substance. The stoichiometry of Reaction 1 is controlled precisely via control
647 of concentrations and flow rates of the feeds. Conversion of starting materials to Intermediate 1

648 with minimal impurity formation is ensured through control of the reaction temperature. Reaction
649 2 is controlled through feedback control of the addition rate of Intermediate 2 based on the PAT
650 measurement of Intermediate 1 levels. This ensures correct stoichiometry for that reaction and
651 minimises the impact of variability of the Intermediate 1 feed solution on drug substance purity.
652 The PAT also measures levels of crude drug substance and process impurities, which confirm
653 successful operation of all preceding steps and consistent product quality.

654
655 RTD was used to develop a suitable strategy for disturbance detection, corrective actions, and
656 material diversion. RTD characterisation was based on mathematical modeling of all unit
657 operations and surge points across the entire CM process over planned mass flow rates. The RTD
658 was then confirmed through experimental tracer studies for appropriate segments of the
659 commercial equipment. Decisions for triggering material diversion are based on comparing
660 process parameters and PAT measurements to predefined acceptance criteria with timing and
661 duration of diversion informed by the RTD. Importantly, the RTD is also used for material
662 traceability purposes.

663
664 Understanding of process dynamics and its impact on quality attributes of material produced
665 throughout the entire process was also used to guide start-up and shutdown strategies. For example,
666 during start-up of Reactions 1 and 2, a small amount of Intermediate 1 or crude drug substance is
667 diverted at Diversion Points 1 or 2, respectively, to allow those materials to reach the target
668 concentrations before processing into subsequent operations. The criteria for diversion were
669 established based on time considering the RTD. This approach was supported by development
670 studies and confirmed in commercial process equipment. PAT monitoring after Reaction 2
671 provides additional verification that appropriate criteria have been met during start-up. Collection
672 of material proceeds to the end of the process as subsequently described.

673
674 Sampling and process measurement needs were evaluated, considering relevant factors such as
675 residence times (RTs)/RTD, surge points, process dynamics, and the type and purpose of the
676 measurement. The measurement frequency of the PAT at Reaction 2 is sufficient to detect
677 disturbances, inform process adjustments, and ensure timely diversion of material based on
678 predefined criteria. The criteria for material diversion are based on the magnitude and duration of
679 the disturbance, an understanding of process dynamics and RTD for downstream unit operations
680 and surge points, and the impurity purging capability of the crystallisation operation. As a result
681 of this control strategy, all crude drug substance solution that enters continuous crystallisation
682 meets acceptable quality criteria and can be forward processed through the crystalliser.

683
684 Appropriate controls and monitoring requirements for the continuous crystallisation were
685 extensively investigated during development in similar, but smaller scale equipment and verified
686 using commercial equipment. Process development included spiking studies using impurity-
687 enriched feed solutions and intentional perturbations in process parameters (i.e., feed flow rates,
688 their ratios, and temperatures). An evaluation of the encrusted solids in the crystalliser over
689 extended run times demonstrated the solids were the same form and purity as the free-flowing drug
690 substance slurry. The set of process parameters and ranges identified by these studies were
691 appropriately scaled up. Implementation of these controls along with post-crystallisation material
692 tests (e.g., crystal form, purity) ensure consistent quality of the resulting drug substance throughout
693 continuous crystallisation and filtration.

694
 695 The resulting material is collected at Surge Point 3 and is dried and milled using batch operations
 696 to provide a drug substance of the appropriate particle size for use in drug product
 697 manufacturing. Procedures were developed to allow diversion of material at Diversion Points D3
 698 or D4 in the event desired process conditions or material attributes are not met. However, diversion
 699 of the drug substance from the crystalliser was found to be unnecessary either during start-up or
 700 shutdown.

701 **2.3. Consideration of Other Controls**

702 Process robustness and performance over time are important considerations. A risk assessment
 703 was performed to ensure that adequate controls are in place to support the proposed run time
 704 (which can be up to several months). It identified a number of considerations and corresponding
 705 controls/measures. Examples are summarised in Table 2.

706 **Table 2: Examples of other controls for consideration**

Consideration	Controls/Measures
Cleaning and fouling potential	<ul style="list-style-type: none"> • Establishment of a risk-based cleaning strategy, including understanding of the impact of build-up on drug substance quality • Additional monitoring to assess fouling and cleanliness (e.g., pressure sensors at the discharge of feed pumps, periodic visual checks for the continuous crystalliser) • Reduction of other risk factors (e.g., filtering feed streams to further reduce fouling risk)
Stability of in-process materials	<ul style="list-style-type: none"> • Hold times at key points in the process (e.g., feed streams; accumulated material at the surge points, reactors, and crystalliser) managed through batch record and process automation • Risk assessment of microbiological growth (i.e., negligible risk based on the nature of the process materials and conditions)
Calibration and potential for changes/drift in instrumentation	<ul style="list-style-type: none"> • Periodic checks at selected points (e.g., process parameter measurements for the PFR, system suitability for the PAT analyser) • Dual sensors at selected locations (e.g., temperature probes for the PFR) so that appropriate corrective actions can be taken
Equipment maintenance	<ul style="list-style-type: none"> • Maintenance requirements for target run time • Use of redundant equipment (e.g., backup pumps) at key locations to enable continuous operation

708
 709 Additionally, specifications for input materials were evaluated during process development. There
 710 were no differences between batch and continuous processing for this example.

711
 712 Collectively, the process understanding developed along with implementation of the various
 713 controls described provide a robust and reliable control strategy. This ensures consistent quality of
 714 the resulting drug substance including the impurity profile, physicochemical properties, and ability
 715 of the system to identify and appropriately react to unexpected events.

716
 717

718 2.4. Process Validation

719 The combination of process controls, online PAT measurements, comprehensive monitoring of
720 process parameters and material attributes, and end-product testing results in a data-rich
721 environment for this process. Together with system understanding generated during development,
722 this enabled the use of a traditional process validation for commercial product launch and
723 continuous process verification to validate process changes over the product lifecycle.
724

725 A range of batch sizes was initially established based on material demands and the quantities of
726 material necessary to match input needs of the final batch unit operations. The process was
727 validated using a fixed number of batches. A single planned start-up and shutdown of the
728 commercial CM system was used to manufacture the process validation batches. This approach
729 was supported by the totality of evidence demonstrating the start-up and shutdown capabilities of
730 the system. This included development work on similar equipment, commercial equipment and
731 system qualification data, results of a prevalidation demonstration run, and extensive process
732 monitoring of the CM system that can verify success of each start-up and shutdown in real time.
733

734 Subsequently, a continuous process verification approach was adopted after product approval to
735 support increases in batch size with extension of run time. This approach used a risk assessment
736 for the longer run time, which concluded that process performance and material quality would not
737 be impacted. Under the continuous process verification approach, data generated during the
738 manufacture of each batch was used to support successful validation of that batch with the
739 extended run time. This included information such as system performance monitoring and data
740 logs along with other controls that ensure material quality with appropriate detection and corrective
741 action. Additionally, appropriate regulatory actions were taken to communicate this batch size
742 increase with run time change and use of the continuous process verification approach.

743 3. REGULATORY CONSIDERATIONS

744 Refer to Section 4 of the main guideline. In consideration of the specific CM process design,
745 additional elements may need to be included in a dossier. For instance, in this example, the
746 influence of surge points on the material diversion and collection strategy, including the fate of
747 materials, was described.

748 **ANNEX II: CONTINUOUS MANUFACTURING FOR DRUG PRODUCTS**

749

750 **1. INTRODUCTION AND EXAMPLE SYSTEM OVERVIEW**

751 This annex exemplifies one approach to implement CM for a solid dose drug product based on the
 752 scientific principles described in the main guideline. The discussion points presented here are not
 753 exhaustive for solid dose drug product CM systems. Alternative approaches can be used. Specific
 754 considerations relating to the implementation of a continuous direct compression process for a
 755 chemical entity are presented.

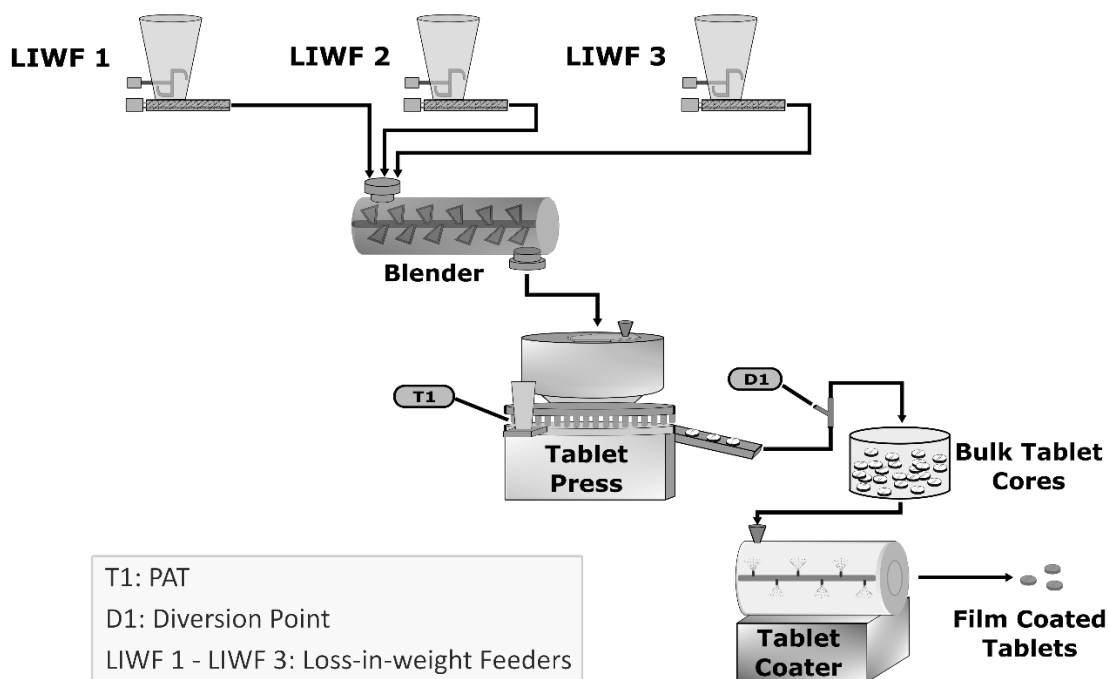
756

757 Figure 2 illustrates a continuous direct compression process that consists of continuous feeding,
 758 blending, and tablet compression unit operations, with batch-mode film coating. It is not intended
 759 to represent a regulatory flow diagram.

760

761 **Figure 2: Example of a solid dose drug product CM system**

762



763

764

765 A PAT tool using an NIR method monitors blend uniformity and triggers tablet diversion. Run
 766 time at a predefined mass flow rate is used to define the batch size range; in this case, the overall
 767 marketing strategy requires batch sizes between 360 and 1080 kg of the drug product.

768 **2. CONTROL STRATEGY AND OTHER TECHNICAL CONSIDERATIONS**

769 The CM system and its control strategy were designed to mitigate the impact of disturbances to
 770 ensure output material quality. The overall control strategy was developed in accordance with the
 771 main guideline and ICH Q8–Q10.

772

773 2.1. Material Characterisation and Control

774 During process development and design, a quality-by-design approach was adopted that identified
775 equipment and process parameters critical to control of the process. Furthermore, the relationships
776 between material quality attributes and their impact on unit operations (particularly the loss-in-
777 weight feeders (LIWFs) and blender) and product critical quality attributes (CQAs) were
778 evaluated. Bulk density of the primary excipient and particle size distribution (PSD) of the drug
779 substance were identified as critical to blend and content uniformity. A defined bulk density range
780 and three-tier (d10, d50, d90) PSD specification were implemented for the excipient and drug
781 substance, respectively.

782 2.2. Equipment Design and Integration

783 Unit operations and system components (e.g., NIR probe) were designed or selected to mitigate
784 the impact of disturbances on final product quality. The overall design principle is, where possible,
785 to use gravity to move material. During system integration, the material flow was coordinated
786 across all unit operations to avoid material accumulation or emptying. System mass balance was
787 obtained through understanding of material flow (i.e., RT and RTD) at the intended operating
788 conditions of each unit operation. The impact of equipment design and operation on process
789 dynamics was characterised by the RTD of individual unit operations, as well as the RTD of
790 process segments between individual unit operations and the diversion point. The RTDs were
791 determined by replacing the drug substance in the formulation with a tracer that has highly similar
792 flow properties to those of the drug substance.

793
794 The following aspects of equipment design and integration were emphasised:
795

- 796 • **LIWF:** Feeder mass flow rates and their variability were characterised. LIWFs are
797 controlled to deliver the theoretical amount of each input material per the formulation; it
798 was demonstrated that the risks of minor variations to product composition were mitigated
799 by blender mixing capability. Feeder mass flow rates were evaluated using design of
800 experiment (DOE) studies and the proven acceptable ranges of target flow rates were
801 defined. Modelling and statistical approaches (e.g., funnel plots) were used to help
802 determine the limits for the magnitude and duration of disturbances in mass flow rates, for
803 which material diversion, operator investigation, or process stop are needed. LIWFs
804 operate in gravimetric mode unless they are refilling (volumetric mode). Refill aspects
805 (e.g., duration and mass of refill) were evaluated to minimise the impact on feeding.
806
- 807 • **Blender:** A horizontal blender was selected for the CM system and the blender design was
808 evaluated (e.g., paddle versus ribbon, number and orientation of paddles in the blender,
809 rotation speed). It was determined that a paddle blender is critical to ensure desired blend
810 uniformity. Rotation speed, number and orientation of the paddles were evaluated for their
811 impact on blend uniformity over the ranges studied, and the corresponding design space
812 for the blending process was defined. RTD characterisation provided information on the
813 degree of forward and back mixing and disturbance propagation, and the RTD was used to
814 define the material traceability and diversion strategy.
815
- 816 • **NIR probe:** The NIR probe was placed in the tablet press feed frame. The chosen NIR
817 equipment met the PAT application requirements (e.g., analysis speed, sampling method,

818 mass flow rate). Probe location and height are fixed; the impact of material build-up was
 819 evaluated and found not significant. The system intended for commercial production was
 820 used to generate data for the development, calibration, and validation of the NIR method.

- 821
- 822 • Diversion point: The RT between the NIR probe and the diversion point was characterised
 823 using a tracer. Using this information, the RTs associated with each unit operation were
 824 determined. The material diversion strategy links LIWF and NIR limits to the RT/RTD
 825 between the LIWF and NIR as well as the RT/RTD between the probe and diversion point,
 826 respectively.
 - 827
 - 828 • Coater: The mass in the coater corresponds to 1 hour of production. Coating was designed
 829 to be complete in 45 minutes; whilst coating, the next aliquot of tablet cores is filled into
 830 the tablet hopper.

831 **2.3. Process Controls and Monitoring**

832 In this system, the LIWFs may introduce fast dynamic disturbances. These may also occur during
 833 changes in operating conditions (e.g., during start-up or process pauses). Therefore, monitoring
 834 and control of these events are important elements of the control strategy. The control strategy
 835 includes NIR measurements, in-process controls (e.g., individual and total flow rates), process
 836 parameters including critical process parameters (e.g., blender rotation speed), and active controls
 837 (e.g., feedback control of tablet weight). The sampling strategy for monitoring and control reflects
 838 the observed process dynamics, therefore ensuring adequate detectability of all relevant
 839 disturbances. Together, these aspects enable proactive control of the system and ensure continuous
 840 operation in a state of control and accurate material diversion to waste based on the predefined
 841 criteria. Unique codes are assigned to predefined batch segments to ensure material traceability
 842 and identification of conforming and non-conforming materials. Start-up/restart, pause/stop, and
 843 shutdown strategies are defined in Table 3.

844
845

Table 3: Start-up/restart, pause/stop, and shutdown strategies

Action	Activity
Start-up/Restart	Material tracking and data collection begins; manufactured material is diverted until it meets the predefined acceptance criteria for material collection.
Pause/Stop	A process pause or stop is executed either manually or automatically, according to predefined criteria.
Shutdown	Material collection continues until manufactured material fails the predefined acceptance criteria, and then the process stops.

846 **2.4. Process Validation**

847 In this example, the continuous process verification approach was adopted, considering elements
 848 such as prior facility experience in implementing a similar CM process and control system (i.e.,
 849 platform approach), availability of product-specific data arising from late-stage product
 850 development using the commercial equipment, the scale independence of the commercial process
 851 (i.e., batch size varies by run time), a comprehensive control strategy with high-frequency data
 852 collection, and the use of real-time data from every manufacturing run to further support
 853 continuous process verification. The control strategy provides real-time monitoring, trending, and

854 prediction analysis through the use of NIR measurements, LIWF data, and other data sources
855 arising from monitoring process parameters (e.g., blender torque), thus providing a high degree of
856 assurance of real-time CM system stability and performance and output material quality. The
857 continuous process verification approach, coupled with appropriate regulatory action for reporting
858 manufacturing changes, was used to validate run time extensions beyond current experience.

859 **3. REGULATORY CONSIDERATIONS**

860 Refer to Section 4 of the main guideline. In consideration of the specific CM process design,
861 additional elements may need to be included in a dossier. For instance, in this example, elements
862 that can significantly impact process dynamics and homogeneity (e.g., design space, number of
863 paddles and their orientation in the horizontal paddle blender) were described.

864 **ANNEX III: CONTINUOUS MANUFACTURING OF THERAPEUTIC PROTEIN DRUG**
 865 **SUBSTANCES**

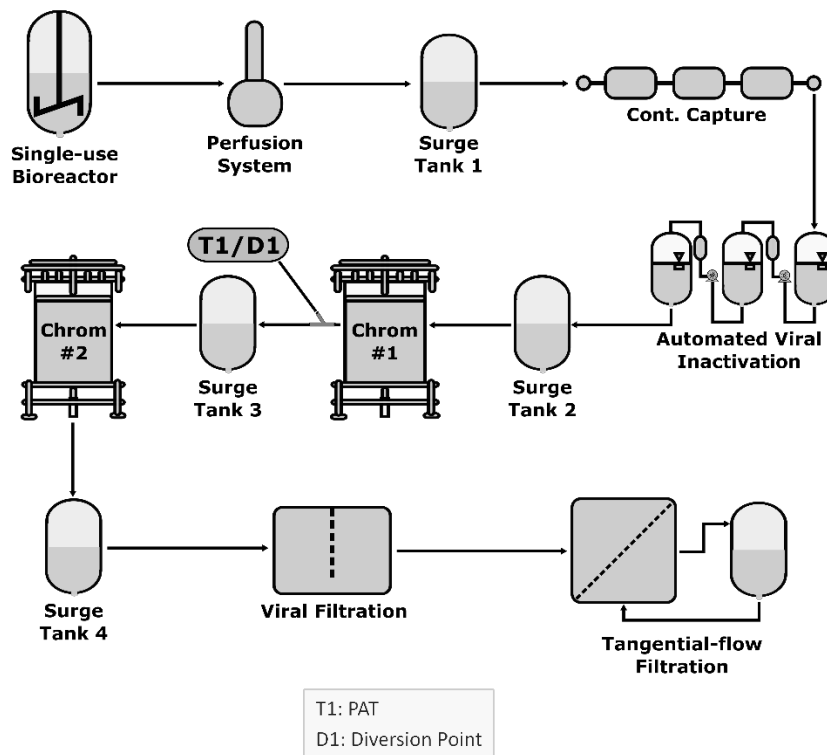
866
 867 **1. INTRODUCTION AND EXAMPLE SYSTEM OVERVIEW**

868 This annex augments the main guideline by providing additional considerations specific to CM
 869 processes for therapeutic protein drug substances and drug substances used as intermediates for
 870 subsequent conjugation (e.g., pegylation). It describes aspects that could be applied in fully or
 871 partially integrated CM systems. The discussion points presented below are not exhaustive.
 872 Alternative approaches can be used.

873
 874 Figure 3 shows an example of a fully continuous drug substance process for therapeutic proteins
 875 (e.g., monoclonal antibodies). It is not intended to represent a regulatory flow diagram. This
 876 process integrates a perfusion cell culture bioreactor with continuous downstream chromatography
 877 and other purification steps to continuously capture and purify the target protein. Each individual
 878 unit operation is integrated with adjacent unit operations, or a surge tank is used in a connection
 879 between unit operations. Using a surge tank or line allows continuous operations to accommodate
 880 differences in mass flow rates or process dynamics. Other examples of CM systems may use
 881 integrated unit operations for selected steps.

882
 883 In CM processes, a single thaw of one or multiple vials from the same cell bank may result in
 884 either a single harvest or multiple harvests. This produces a single batch or multiple batches of
 885 drug substance.

886
 887 **Figure 3: Example of a drug substance CM system for therapeutic proteins**
 888



889

890 2. CONTROL STRATEGY

891 2.1. Adventitious Agent Control

892 In general, all principles used to ensure safety in batch manufacturing are applicable to CM. Safety
893 is demonstrated by a threefold approach based on the principles outlined in ICH Q5A. Control of
894 adventitious agents (e.g., bacteria, viruses, fungi, mycoplasma) should be based on a risk
895 assessment of all potential sources of contamination (e.g., starting and raw materials,
896 manufacturing operations), the ability of the process to remove and inactivate adventitious agents,
897 and the testing capability to ensure the absence of adventitious agents. Based on this assessment,
898 a strategy should be developed to include the type and frequency of adventitious agent testing
899 undertaken to demonstrate that the process remains free of contamination during cell culture and
900 other downstream steps. An aspect unique to CM is extended cell culture duration and continuous
901 processing of harvested cell culture material to obtain drug substances. This means that measures
902 should be in place to demonstrate the acceptability of all cell culture material used to generate a
903 given drug substance batch. Rapid testing for adventitious agents, when possible, may enable real-
904 time decision-making to mitigate the impact of contamination events during continuous operation.

905 2.2. Equipment Design and System Integration

906 While the use of closed processing equipment may decrease the risk of contamination from
907 adventitious agents, the integrity of single-use equipment during use should be ensured to prevent
908 contamination. The potential weak points (e.g., welds, connectors) and typical locations where
909 single-use systems require changing out over a potentially extended time frame or at a higher
910 frequency for a CM process should be evaluated for potential contamination risks. Filtration steps
911 in CM may be subject to longer filtration periods and potentially increased throughput per unit
912 area or a greater number of filter changes than those under batch manufacturing. Given these
913 factors, a control strategy and a clearly defined scheme should be put in place to allow for filter
914 changes and post-use integrity testing, as appropriate, without interrupting the process. In the event
915 of a filter failure, a clear strategy for material diversion and refiltration (reprocessing) should be
916 defined.

917
918 The CM system should contain appropriate sampling locations based on risk assessment to enable
919 detection of inadvertent contamination, while avoiding unnecessary contamination risk introduced
920 through the sampling procedure. The sampling locations and frequency may be adjusted based on
921 improved product and process understanding.

922
923 Integrated systems may use surge tanks for flow rate adjustments or other purposes between steps
924 such as virus inactivation. When surge tanks are used, the relevant RTD, uniformity and microbial
925 risks to the product in these surge tanks should be evaluated and defined in advance.

926
927 When considering the facility design for a CM process, either closed systems in an open
928 architecture (ballroom) layout or open systems with physical segregation of post-viral filtration
929 material could be used with appropriate justification.

930 2.3. Process Monitoring and Real-Time Release Testing

931 CM lends itself to various monitoring schemes with different levels of automation. Examples
932 include in-line sensors placed directly in a process vessel or flowing material stream and online

933 analysers that conduct automatic sampling. Regardless of the approach used, appropriate
934 monitoring at suitable stages of the CM process enables timely data analysis to ensure operations
935 are in a state of control. In certain cases, relevant process parameters may be adjusted to ensure
936 the quality of in-process or output materials. Enhancing in-line/online PAT capabilities and
937 development of automation systems for process monitoring enables a continuous monitoring
938 scheme in support of a release testing strategy that may include RTRT for some quality attributes.
939 Conventional offline testing for product release is necessary for quality attributes for which
940 analytical technologies are not available for online or in-line measurements (e.g., potency).
941 Likewise, conventional tests for monitoring and control (e.g., microbiological analytical methods
942 and other tests that require long processing times) might also be needed.

943 3. PROCESS VALIDATION

944 3.1. Approaches to Process Validation

945 Process validation approaches used for processes run in batch mode are also applicable to CM
946 processes. Therefore, the scope of validation continues to be to demonstrate the ability to
947 consistently manufacture a product with the desired quality attributes.

948
949 For therapeutic protein CM, any approach chosen to demonstrate the consistency of process
950 performance and product quality should consider all potential sources of variability. This may
951 include variability between batches purified from harvest materials collected up to the limit of *in*
952 *vitro* cell age from a single cell bank thaw, as well as the potential variability between different
953 batches purified from harvests of multiple cell bank thaws. Variability may be evaluated either as
954 part of process qualification or through alternative studies, if justified. For some unit operations,
955 the use of scale-down models remains an alternative approach to validation (e.g., viral clearance),
956 if justified.

957
958 Alternatives to the process validation approaches (e.g., continuous process verification) may be
959 considered when justified. Refer to Sections 3.3 and 4.7 of the main guideline for more details
960 regarding continuous process verification. Additionally, elements such as risk assessment, the
961 applicability of small-scale development data, process models, and experience with molecules that
962 are sufficiently alike with respect to their CM process may be considered in determining the
963 suitability of a continuous process verification approach.

964 3.2. Run Time Considerations

965 Bioreactors for CM may operate for significantly longer periods of time than bioreactors for batch
966 manufacturing. The approach to establish a limit of *in vitro* cell age for production cells does not
967 differ, regardless of the mode of bioreactor operation. Previously established limits of *in vitro* cell
968 age for a bioreactor operating in a batch mode run may not be applicable to a bioreactor operating
969 in a continuous mode under different culture conditions. The limit of *in vitro* cell age used for
970 production should be based on data derived from production cells expanded under pilot-plant scale
971 or commercial-scale conditions to the proposed *in vitro* cell age or beyond as outlined in ICH Q5A.

972
973 Run time considerations should include factors such as the control of all adventitious agents (e.g.,
974 viruses, bacteria, fungi, mycoplasma) and the impact of resin and membrane lifetimes. Viral testing
975 should be conducted as outlined by ICH Q5A, and an appropriate microbial control strategy should
976 be established.

977 **3.3. Viral Clearance Validation**

978 The general recommendations outlined in ICH Q5A for viral safety and clearance remain
979 applicable for CM. Where recommendations may not be applicable to a CM system, scientifically
980 justified alternatives may be proposed.

981
982 Considerations relevant to CM in aspects such as qualification of small-scale models are addressed
983 in ICH Q5A.

984 **ANNEX IV: INTEGRATED DRUG SUBSTANCE AND DRUG PRODUCT**
985 **CONTINUOUS MANUFACTURING**

986
987 **1. INTRODUCTION**

988 This annex augments the main guideline by providing additional considerations for the
989 development and implementation of an integrated drug substance and drug product CM process
990 (referred to as integrated process hereafter). An integrated process for a small molecule tablet
991 dosage form is used for illustration. The illustrative example and approaches described in this
992 annex are not exhaustive. Alternative approaches can be used.

993 **2. INTEGRATED SMALL MOLECULE DRUG SUBSTANCE/DRUG PRODUCT**
994 **PROCESSES**

995 **2.1. Characteristics of Drug Substance and Drug Product Process Steps**

996 Considering the differences between the drug substance and drug product process steps enables
997 appropriate design of an integrated process. For example, process steps for drug substance and
998 drug product manufacturing may have different RTs, and a prevalence for liquid or solid input
999 material addition can lead to a different frequency of in-process measurements. These differences
1000 may influence the selection of equipment, equipment connections, surge lines or tanks, and the
1001 locations of in-process measurements and material diversion.

1002 **2.2. Example of an Integrated Process**

1003 Figure 4, which is not intended to represent a regulatory flow diagram, illustrates a fully continuous
1004 integrated drug substance and drug product process. It shows the following elements:

- 1005
- 1006 • Material addition points for liquids and solids
 - 1007
 - 1008 • Each process step used for drug substance and drug product manufacturing
 - 1009
 - 1010 • Process design for the interface between the drug substance and drug product
 - 1011
 - 1012 • Sampling locations for all in-line/at-line/offline measurements, including PAT (shown by
1013 T1–T5)
 - 1014
 - 1015 • All diversion points (shown by D1–D4)
 - 1016

1017 In this example, chemical reaction using flow reactors, continuous crystallisation and crossflow
1018 filtration are used to obtain the drug substance as a highly concentrated crystal slurry. The selection
1019 of a wet granulation process for the manufacture of tablet drug products permits the drug substance
1020 and drug product processes to be integrated through the continuous filtration line. The concentrated
1021 crystal slurry functions as both the drug substance source and the granulation fluid. No surge lines
1022 or tanks are used.

1023
1024 Other process schemes—including, for example, different purification methods, surge tanks, mix
1025 of batch and continuous unit operations—could also be used in the design of an integrated process.
1026 If the process design does not involve isolation of crystals, then details should be provided on how

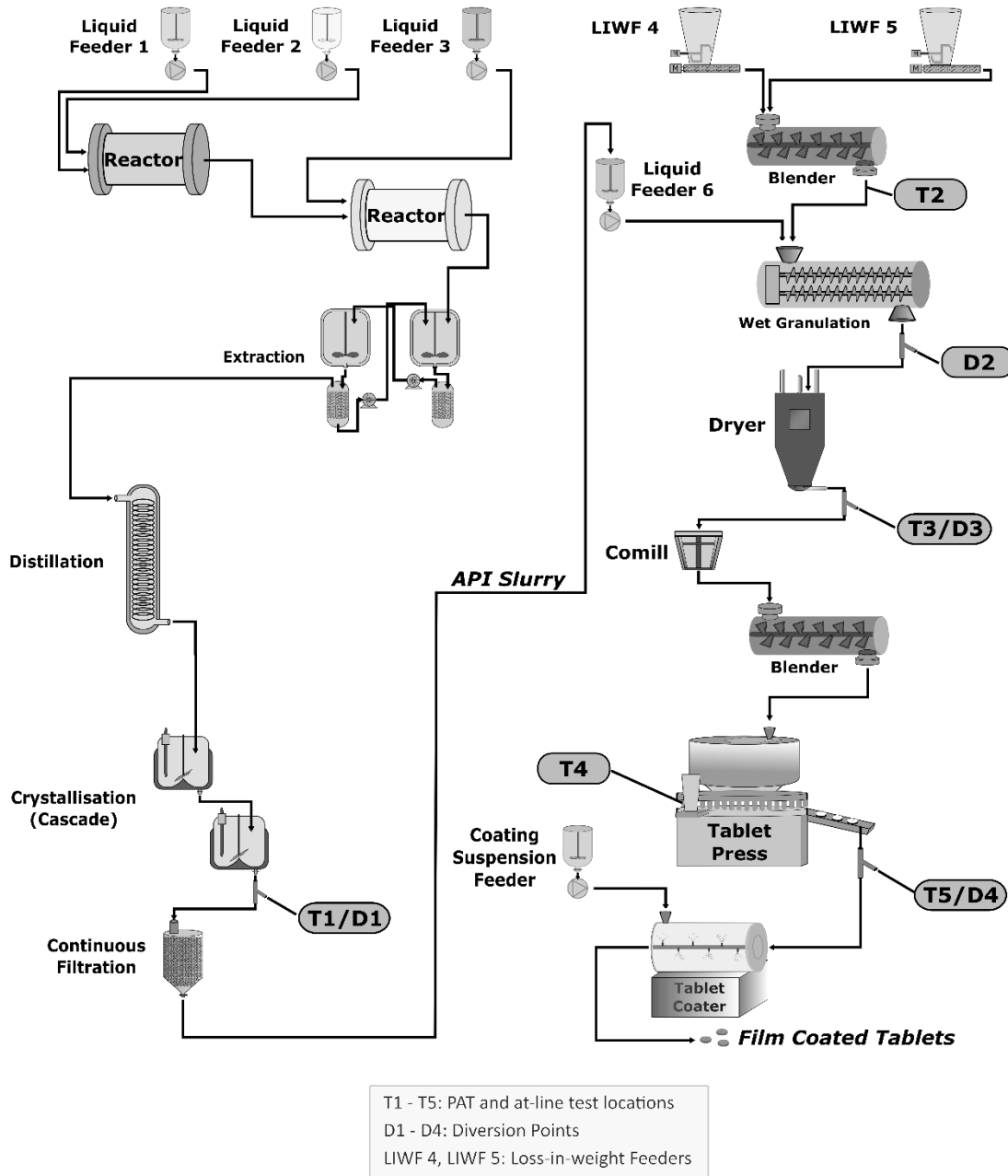
1027 drug substance purity is ensured.

1028

1029

1030

Figure 4: Example of an integrated drug substance and drug product CM system



1031

1032

1033 2.3. Process Design, Monitoring and Control

1034 Figure 4 illustrates how the monitoring points create several process segments (i.e., from the first
 1035 drug substance reactor up to location T1, process steps from T1 to T2, etc.). The sampling strategy
 1036 could be based on RTD characterisation of individual steps, process segments, or the entire
 1037 process. In this example, the RT/RTD of the drug substance process segment provides a suitable

1038 time frame to monitor drug substance quality in real time, considering an appropriate sampling
1039 frequency, test method, time needed for measurement, and instrument capability. Location T1/D1
1040 is used for sampling drug substance for offline testing or for diversion of drug substance, as
1041 necessary. Diversion of material impacts mass flow and may require a compensation strategy in
1042 the downstream operations considering the RTD.

1043
1044 Allowable variations (including minor disturbances) identified through DOE or other suitable
1045 studies are incorporated into the process control strategy. For example, the process parameter
1046 ranges for material additions and reactors, as well as the magnitude and duration of an allowable
1047 disturbance, could be based on the variations shown to be within the purification capability of the
1048 crystallisation step, so there would be no adverse impact on the drug substance purity and impurity
1049 profile. An additional risk-based safety margin is included in the established thresholds to ensure
1050 all non-conforming material is diverted. Variations outside these thresholds result in material
1051 diversion using a suitable method for material traceability (e.g., RTD model).

1052
1053 Ongoing assessment of equipment performance helps predict and prevent potential problems and
1054 ensures the ability of a CM process to operate as intended over time. Two such examples are: (1)
1055 during continuous filtration, monitoring filter back pressure to evaluate filter saturation (maximum
1056 pressure) and prevent filter failure; and (2) during material feeding using LIWFs, monitoring the
1057 feeder screw speed in relation to its maximum capacity to inform low feeder fill-level. Monitoring
1058 of equipment performance could be used to support how process control will be ensured, especially
1059 during long run times.

1060 **2.4. Start-up and Shutdown**

1061 Individual unit operations of an integrated drug substance and drug product process could achieve
1062 its desired operating conditions at different times due to differences in the type of transformation
1063 (e.g., chemical versus physical transformation) and the RT in the equipment. When such
1064 differences occur, careful planning of start-up and shutdown sequences enables faster product
1065 collection and reduces waste.

1066 **2.5. RTD Characterisation for System Dynamics and Material Traceability**

1067 Refer to the main guideline for RTD characterisation. An integrated process may use different
1068 approaches or tracers to characterise various process segments considering aspects such as liquid
1069 and solid flow streams.

1070 **3. SPECIFICATION AND BATCH DATA**

1071 **3.1. Drug Substance Specification**

1072 Even though the drug substance is not isolated in an integrated drug substance and drug product
1073 process, a drug substance specification should be defined and justified in accordance with ICH
1074 Q6A and other relevant ICH guidelines. Institution of a drug substance specification defines the
1075 quality of the drug substance, as well as facilitates the management of lifecycle activities (e.g.,
1076 facility changes), investigation of adverse events and product recalls, and development of
1077 pharmacopeial monographs.

1078

1079 Although a drug substance specification should be instituted, drug substance testing may not be
1080 required on a routine basis when the integrated process is appropriately controlled. A set of process
1081 performance criteria can be defined such that the drug substance could be considered “conforms
1082 to specification, if tested” when those process performance criteria are met. To ensure there is a
1083 comprehensive monitoring of the quality of the drug substance during the lifecycle of the product,
1084 conformance to the drug substance specification should be verified on a periodic and event-driven
1085 basis by testing the purified drug substance at an appropriate location using a relevant sampling
1086 plan. The frequency of the periodic verification should be defined and justified. Drug substance
1087 periodic verification can be based on the frequency of drug product production and time. Event-
1088 based verifications could be triggered by a change in supplier, starting material, synthesis
1089 conditions, or other factors considering risk. Refer to ICH Q6A for additional details on periodic
1090 testing.

1091
1092 Appropriate sampling locations should be incorporated into the process design to enable testing of
1093 the drug substance (e.g., location T1 in Figure 4). Any modifications made to the sample to enable
1094 the test (e.g., drying of the crystal slurry for testing crystalline form) may be incorporated into the
1095 test methodology. Sampling locations should be identified in the drug substance specification.

1096
1097 Although the drug substance is not isolated, a discussion of the origin and fate of potential
1098 impurities (e.g., related substances, residual solvents, catalysts), robustness of impurity clearance,
1099 and impurity carryover from the drug substance into the drug product should be provided in the
1100 dossier. The control of impurities formation and clearance should be integrated into the overall
1101 control strategy.

1102 **3.2. Drug Product Specification**

1103 In integrated processes, attributes typically associated with the drug substance quality are generally
1104 included in the drug product specification unless justified per ICH Q6A. Therefore, the drug
1105 product specification in an integrated process is more extensive than that of a batch process and
1106 may include drug substance related substances, residual solvents (used in drug substance
1107 synthesis), elemental impurities, etc., when appropriate. The specified impurities in the drug
1108 product specification may differ from the specified impurities in the drug substance specification
1109 (e.g., mutagenic impurity).

1110
1111 Sampling location should be appropriately identified in the drug product specification table, as
1112 some testing (e.g., testing for drug substance periodic verification as described above) may need
1113 to be performed following the drug substance purification step (before drug product formation).

1114
1115 An example of a drug substance and drug product testing approach for an integrated process is
1116 shown in Table 4. The test attributes listed are considered relevant for this example. The specific
1117 details of each integrated process should be considered in the selection of the appropriate test
1118 attributes and testing plan.

1119

1120

Table 4: Example of a testing approach for an integrated CM

Test Attribute ¹	Drug Substance Specification for Periodic Testing		Drug Product Specification for Routine Testing of Every Batch	
	Test	Sampling Location ²	Test	Sampling Location ²
Description	N/A	N/A	✓	Coated tablets
Identity	✓	Use drug product test result	✓	PAT at tablet feed frame (T4)
Crystalline Form ³	✓	Sampling Location T1	N/A	Not tested when justified
Chirality ⁴	✓	Sampling Location T1	N/A	Not tested when justified
Particle Size	✓	Sampling Location T1	N/A	Not tested
Purity	✓	Sampling Location T1	N/A	Not tested
Assay	N/A		✓	Core tablets, Sampling Location combination of T4 (blend uniformity) and T5 (tablet weight)
Impurities	<i>Impurity specification for drug substances and drug products may differ</i>			
<i>Related Substance</i>	✓	Sampling Location T1 (at-line high performance liquid chromatography (HPLC)) ²	✓	Sampling Location T1 (at-line HPLC) ² or Coated Tablets (offline HPLC testing), as appropriate
<i>Residual Solvents</i>	✓		✓	
<i>Elemental Impurities</i>	✓		✓	
<i>Mutagenic Impurities</i>	✓		✓	
Dissolution	N/A	N/A	✓	Coated Tablets
Uniformity of dosage units	N/A	N/A	✓	Uncoated Tablets
Water content	N/A	N/A	✓	Coated Tablets
Microbial limits	N/A	N/A	✓	Coated Tablets

1121 ¹ Include tests that are necessary to ensure the identity, strength, quality and purity of the drug substance and
 1122 bioavailability of the drug product as per ICH Q6A.

1123 ² Tests that are common to both drug substance and drug product specification need to be tested only once; the same
 1124 test result can be used for the drug substance and drug product.

1125 ³ In this example, crystalline form is considered a critical quality attribute for the drug substance and hence tested
 1126 periodically. Crystalline form is not tested in the drug product as lack of form change during drug product
 1127 processing has been demonstrated.

1128 ⁴ In this example, chirality is considered a critical quality attribute for the drug substance.

1129 3.3. Batch Data

1130 Although the drug substance is not isolated, small, planned diversions during process development
 1131 could be used to obtain batch data that is representative of commercial drug substance.

1132 4. STABILITY REQUIREMENTS

1133 4.1. Drug Substance Stability

1134 Drug substance stability data to define a re-test period is not applicable as the drug substance is
 1135 not isolated and stored in an integrated process. However, institution of a hold time enables

1136 temporary storage of drug substance during an interruption in production. In the absence of data
1137 to support a hold time, drug substance formed during a process interruption should be discarded.
1138 Drug substance stability data may be appropriate for other aspects, such as to support the storage
1139 of in-house reference standards and to gain an understanding of product stability profiles.

1140 **4.2. Drug Product Stability**

1141 The ICH stability guidelines and Section 4.5 of the main guideline are applicable.

1142 **5. LOCATION OF DRUG SUBSTANCE AND DRUG PRODUCT INFORMATION IN**
1143 **THE CTD**

1144 Drug substance and drug product information could be provided in the respective CTD sections
1145 3.2.S and 3.2.P of the dossier as per ICH M4Q. A description of the process step that integrates
1146 the drug substance and drug product could be based on its relevancy to the respective section. For
1147 example, in the process example provided in this annex, the continuous filtration process could be
1148 described in CTD section 3.2.S as it is related to concentration of the drug substance. The
1149 integrated flow diagram can be provided in CTD section 3.2.P and referenced in section 3.2.S.

1150 **ANNEX V: PERSPECTIVES ON MANAGING DISTURBANCES**

1151

1152 **1. INTRODUCTION**

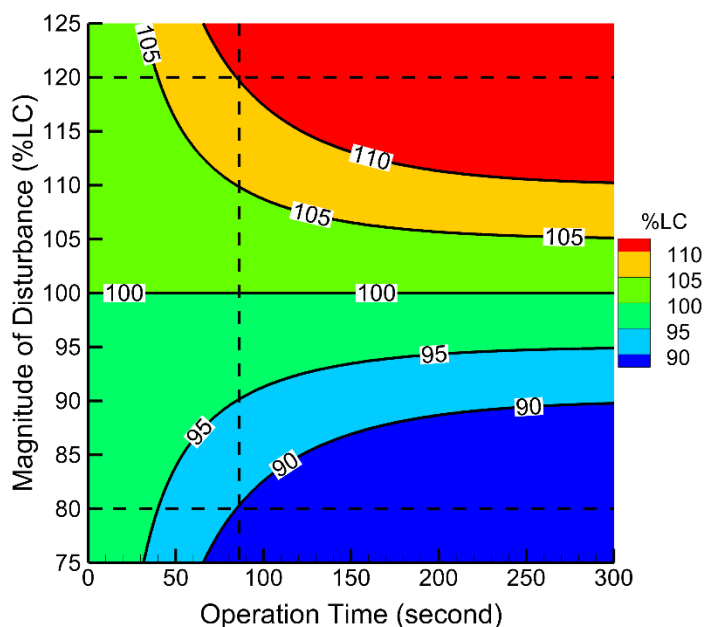
1153 This annex describes examples of approaches for managing transient disturbances (hereafter
 1154 referred to as disturbances in this annex) that may occur during CM. The discussion points
 1155 presented here are not exhaustive. Alternative approaches can be used.

1156 **2. BACKGROUND**

1157 Disturbances may result in product quality variation. Some quality variations in an earlier process
 1158 step may be resolved by downstream process steps. The extent of quality variations and the ability
 1159 to resolve them in subsequent steps are impacted by the amplitude, duration, and frequency of the
 1160 disturbance. Identification of tolerable ranges for these parameters and establishing appropriate
 1161 acceptance criteria will enable the development of an effective strategy for managing disturbances.
 1162

1163 Manufacturers may use various methodologies (e.g., DOE, RTD studies or a combination of both)
 1164 to understand the impact of disturbances. Funnel plot predictions based on an RTD model can be
 1165 a useful tool to understand the qualitative and quantitative impact of the amplitude and duration of
 1166 a disturbance on material quality. Figure 5 shows a funnel plot for drug substance feeding in a drug
 1167 product CM process (similar to the example in Annex II). Funnel plots are specific to the
 1168 formulation and process conditions used in RTD model development. Information from the funnel
 1169 plots helps to inform the selection of appropriate acceptance criteria for disturbances. For example,
 1170 the dotted lines in the following funnel plot show that a disturbance of +/- 20% lasting less than
 1171 90 seconds would not cause the drug concentration in the blend to exceed the 90–110% label claim
 1172 (LC).
 1173
 1174

Figure 5: Example of a funnel plot for the feeding of a drug substance



1175
 1176

1177 **3. MANAGEMENT OF DISTURBANCES**

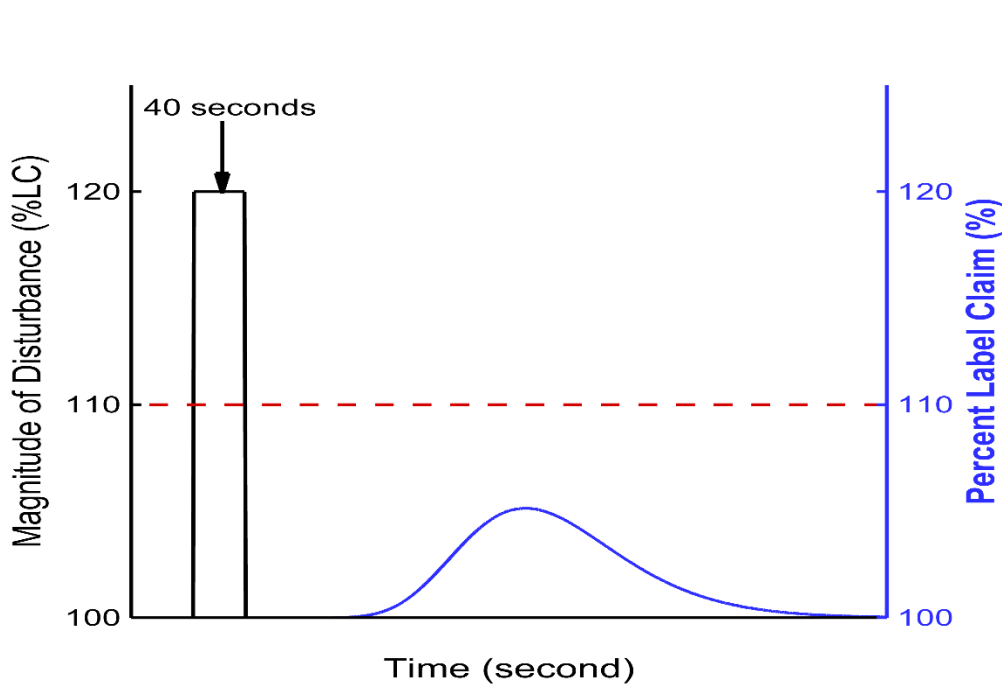
1178 Manufacturers may develop various approaches to manage disturbances considering the specific
 1179 details of the CM system and risks of a disturbance. Three examples considering different risks of
 1180 a disturbance are provided below:

- 1181
- 1182 • Example 1: The amplitude and duration of the disturbance meet predefined acceptance
 1183 criteria for the disturbance, and the occurrence of such disturbances is infrequent.
 1184
- 1185 • Example 2: The amplitude or duration of the disturbance exceed the predefined acceptance
 1186 criteria for the disturbance, and the occurrence of such disturbances is infrequent.
 1187
- 1188 • Example 3: The amplitude and duration of each disturbance meets predefined acceptance
 1189 criteria for the disturbance, but multiple, frequent disturbances are observed.
 1190

1191 These common examples focus on the impact of disturbance from an LIWF on the drug
 1192 concentration in the blend for a CM process similar to that described in Annex II, given that all
 1193 other parameters being monitored meet the predefined acceptance criteria. These examples use the
 1194 information in the funnel plot (Figure 5) and, for the purpose of discussion, assume that the
 1195 acceptance criteria for the magnitude and duration of an LIWF disturbance is +/- 20% lasting for
 1196 80 minutes. These examples help illustrate the important considerations in management of
 1197 disturbances under selected scenarios, which may also be applicable to drug substances and other
 1198 CM processes.

1199 **3.1. Disturbance Example 1**

1200 **Figure 6: Example of an infrequent disturbance that is within the acceptance criteria for**
 1201 **disturbances**



1202
 1203

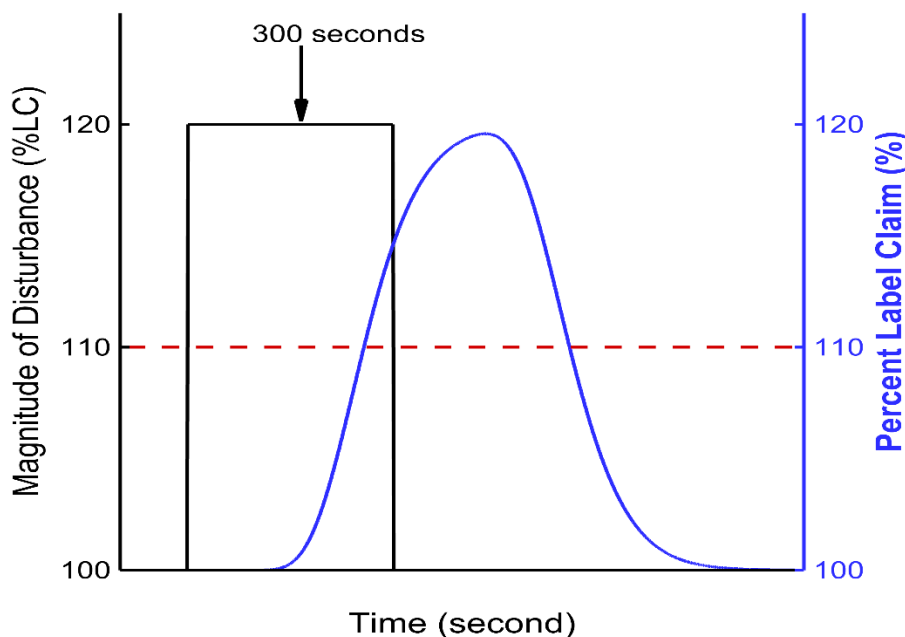
1204 Description: Figure 6 illustrates a drug substance LIWF with an infrequent transient +20% flow
 1205 spike lasting 40 seconds, which is within the predefined acceptance criteria for disturbances. This
 1206 disturbance causes an increase in the amount of the drug substance fed into the blender, before
 1207 returning to normal operating condition. The funnel plot (Figure 5) shows that following this
 1208 disturbance, the drug substance concentration in the blend remains within the 90–110% acceptance
 1209 criteria, due to back mixing. An additional quality check, such as measurement of the drug
 1210 substance concentration at a suitable location (i.e., NIR measurements at the tablet press feed
 1211 frame), confirms the blend is within 90–110%.

1212
 1213 Impact: Although this disturbance represents an excursion from normal operation, the quality of
 1214 the output material is not affected as the magnitude/amplitude of the disturbance and product
 1215 quality meet their predefined acceptance criteria.

1216
 1217 Action: No material is diverted. Collection of the output material continues, and the process
 1218 continues to operate. No investigation is needed, because such a disturbance has been evaluated
 1219 during development and its origin and impact on material quality are understood.

1220 **3.2. Disturbance Example 2**

1221 **Figure 7: Example of an infrequent disturbance that is outside the acceptance criteria for**
 1222 **disturbances**



1223
 1224
 1225 Description: Figure 7 illustrates a drug substance LIWF with an infrequent transient +20% flow
 1226 spike lasting 300 seconds. The disturbance is outside the predefined acceptance criteria for
 1227 disturbances. This disturbance causes an increase in the amount of the drug substance fed into the
 1228 blender before returning to normal operating condition. The funnel plot (Figure 5) shows that
 1229 following this disturbance, the drug substance concentration in the blend exceeds the 90–110%
 1230 acceptance criterion. An additional quality check, such as measurement of the drug substance

1231 concentration at a suitable location (e.g., NIR measurements at the tablet press feed frame),
 1232 confirms the blend exceeds 110%.

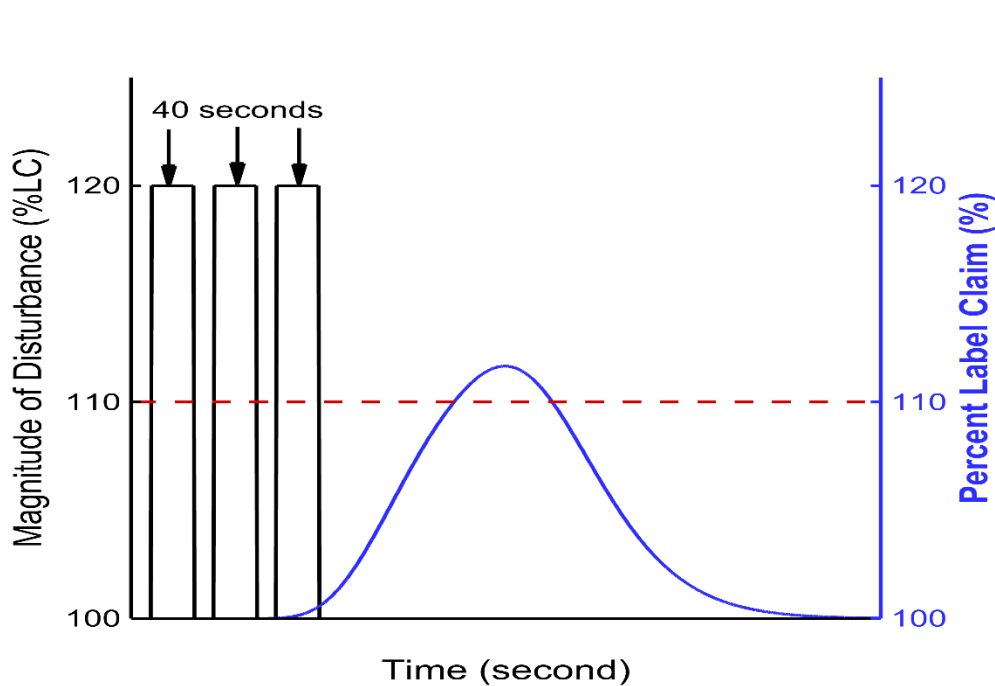
1233
 1234 **Impact:** The quality of the output material is adversely impacted as the disturbance duration
 1235 exceeds the predefined acceptance criteria.
 1236

1237 **Action:** The process continues to operate while the non-conforming material is diverted according
 1238 to a pre-established procedure, and the time to start and end diversion is controlled by the
 1239 automation system. The system returns to normal material collection mode when the non-
 1240 conforming material is completely diverted. A concurrent investigation should be initiated to
 1241 determine root cause.
 1242

1243 **Diverted Amount:** The amount of material diverted depends on the control strategy used (including
 1244 specific triggers for material diversion) and on the process dynamics from the point of disturbance
 1245 detection and the point at which material diversion ends. Inclusion of confidence intervals in the
 1246 RTD provides a safety margin to ensure all non-conforming material is diverted from the batch.
 1247 Additional factors, such as the sampling strategy and the ability to trace and remove materials, are
 1248 considered in establishing the criteria for material diversion.

1249 **3.3. Disturbance Example 3**

1250 **Figure 8: Example of disturbances that are within the acceptance criteria for disturbances,**
 1251 **but occur frequently**



1252
 1253
 1254 **Description:** Figure 8 illustrates a drug substance LIWF with multiple frequent transient +20%
 1255 flow spikes, each lasting 40 seconds, resulting in variability in the amount of material fed into the
 1256 blender.
 1257

1258 **Impact:** Although each disturbance meets the predefined acceptance criteria for disturbances, they
 1259 occur with a high frequency over a short time period. In this example, the system cannot dampen
 1260 these multiple disturbances sufficiently, thus resulting in non-conforming materials.

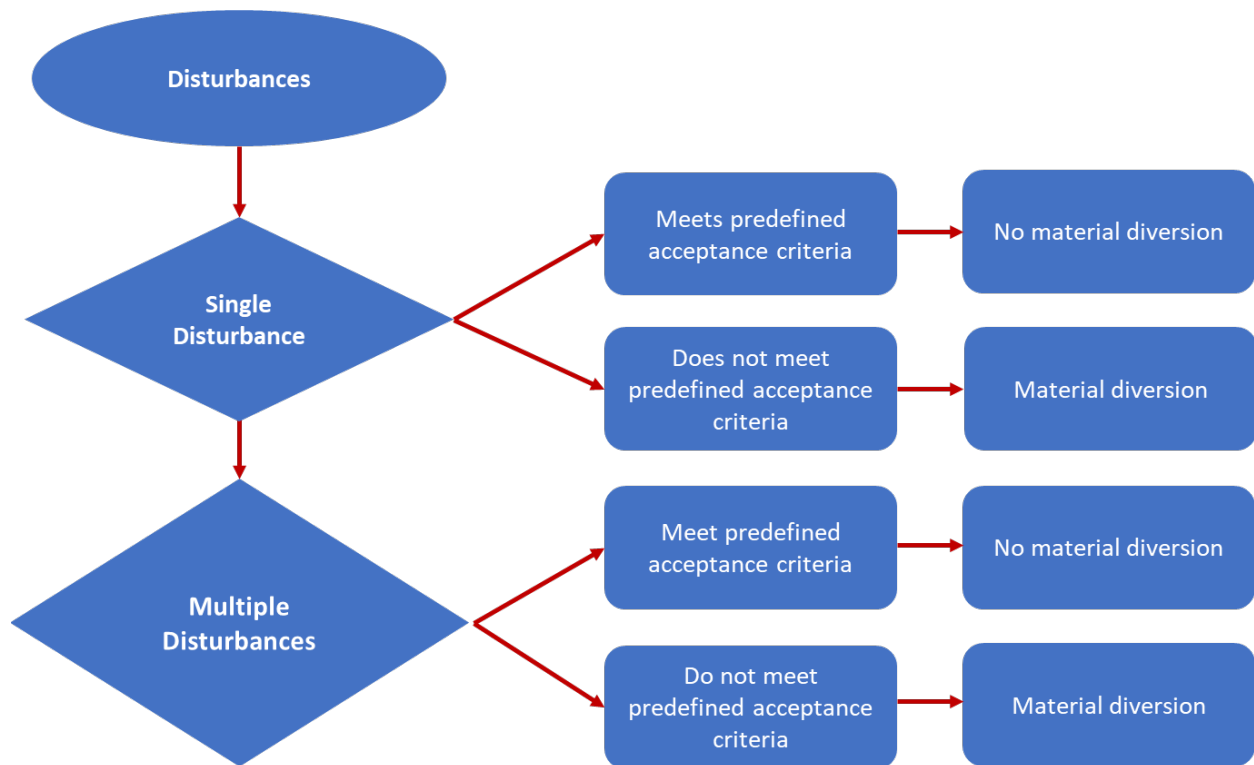
1261
 1262 **Action:** The impact of these disturbances on system performance and output material quality is
 1263 monitored closely (e.g., NIR method, other elements of the control strategy). Process operation
 1264 and product collection continue until one or more elements of the control strategy do not meet the
 1265 predefined acceptance criteria. When a criterion is no longer met, the material is diverted according
 1266 to a pre-established procedure. If high-frequency disturbances persist, process operation may be
 1267 paused. An investigation is conducted to understand the root cause for these frequent disturbances.
 1268 Such investigations enable preventative actions to be taken to avoid equipment failure and adverse
 1269 impact on critical quality attributes, ensure process performance (e.g., robustness), etc. Assessment
 1270 of process capability or other evaluations may also be warranted. Setting acceptance criteria for the
 1271 frequency of disturbances could also be considered to aid the management of disturbances.
 1272

1273 **Diverted Amount:** The amount diverted is the same as described in Section 3.2 of this annex. The
 1274 disposition of the diverted material and the entire batch is assessed upon completion of the
 1275 investigation.

1276 **3.4. Summary**

1277 Figure 9 outlines the likely scenarios, possible risks, and mitigation strategies of the above three
 1278 examples.

1279
 1280 **Figure 9: Decision tree for material diversion**
 1281



1282