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Standard Guide for Application of Continuous Manufacturing (CM) in the Pharmaceutical Industry[1]

This standard is issued under the fixed designation E2968; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This guide introduces key concepts and principles to assist in the appropriate selection, development and operation of CM technologies for the manufacture of pharmaceutical products. Athough selected concepts covered here can be applied to biopharmaceutical CM (BioCM), the focus of this guide is on non-biopharmaceutical applications.

1.2 Particular consideration is given to the development and application of the appropriate scientific understanding and engineering principles that differentiate CM from traditional batch manufacturing.

1.3 Most of the underlying concepts and principles (for example, process dynamics and process control) outlined in this guide can be applied to both Drug Substance (DS) and Drug Product (DP) processes. However, it should be recognized that in Drug Substance production the emphasis may be more on chemical behavior and dynamics in a fluid phase whereas for solid drug product manufacture there may be a greater emphasis on the physical behavior and dynamics in a solid/powder format.

1.4 This guide is also intended to apply in both the development of new processes, or the redesign of existing ones.

1.5 All values are stated in SI units. No other units of measurement are included in this standard.

1.6 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.7 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2363 Terminology Relating to Manufacturing of Pharmaceutical and Biopharmaceutical Products in the Pharmaceutical and Biopharmaceutical Industry

E2475 Guide for Process Understanding Related to Pharmaceutical Manufacture and Control

E2537 Guide for Application of Continuous Process Verification to Pharmaceutical and Biopharmaceutical Manufacturing

E2629 Guide for Verification of Process Analytical Technology (PAT) Enabled Control Systems

E2898 Guide for Risk-Based Validation of Analytical Methods for PAT Applications

2.2 *Regulatory Guidance and Other Documents:*

21 CFR 210.3 Current Good Manufacturing Practice in Manufacturing, Processing, Packing or Holding of Drugs, General Definitions[3]

EMA Guideline on process validation for finished products information and data to be provided in regulatory submissions

EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Annex 15: Qualification and Validation

FDA Guidance for Industry PAT A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (2004)[3]

FDA Guidance for Industry Process Validation: General Principles and Practices (2011)[3]

ICH Harmonized Tripartite Guideline, Continuous Manufacturing of Drug Substances and Drug Products, Q13 (Step 2b version, dated 29 July 2021)[4]

ICH Harmonized Tripartite Guideline, Pharmaceutical

[1] This guide is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.11 on Process Design.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, http://www.fda.gov.

[4] Available from International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), ICH Secretariat, Route de Pré-Bois, 20, P.O Box 1894, 1215 Geneva, Switzerland, https://www.ich.org.

Quality System, Q10 (Step 4 version, dated 4 June 2008)[4]

3. Terminology

3.1 *Definitions:*

3.1.1 For general definitions, refer to Terminology E2363 and Guides E2537 and E2475.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *back mixed process*—a process with a residence time distribution (RTD) that is significant compared to the mean residence time. A process where the deviation of a material's residence time distribution from its mean residence time is large enough to indicate significant mixing of materials introduced at a single point into the process at different times.

3.2.1.1 *Discussion*—For example, in a fully back mixed process, quantities of material will be mixed into a single homogeneous condition such that a rapid step change in the properties of inlet material will not result in an equivalent step change in the properties of the output material but will be reflected in a more gradual change. The rate of this change will depend on the material properties, equipment characteristics, residence volume, and the residence time distribution/degree of mixing. A fully back mixed process may be considered and modeled as one or more continuously stirred tank reactors (CSTR) connected in series.

3.2.2 *continuous manufacturing (CM)*——a process where, during normal operation, raw materials are continuously fed into the system at the same time as product is continuously removed from the system. In the context of this guide, continuous manufacturing is considered to be a series of 2 or more continuous, or quasi continuous, transformation steps or unit operations which are integrated into a CM line which may be part of a complete CM plant.

3.2.2.1 *Discussion*—The term continuous process may be used to refer to a single continuous process step or unit operation where the output may not be a finished product. A single continuous process step or unit operation is not considered to be representative of CM as considered by this guide as continuous processes are often used as unit operations within batch (or bin to bin) production.

(1) In a CM process, the degree of transformation of any specific quantity of material from an initial condition into the subsequent condition is a function of the process parameters applied and either:

(a) The position of the material as it flows through the process,

(b) The duration that the material has been within the process, or

(c) A combination of both (a) and (b).

(2) A CM process transforms a pre-defined quantity of material into a pre-defined physical quantity of product which is then subjected to a disposition decision. The amount of expected final product produced is predefined by the amount of starting material but can be divided into separate lots in a flexible way based on principles of science and risk.

(3) Alternatively, CM may be operated with a 'flexible' run-time, in which quantities of product are defined during the operation of the process in a flexible way, based on principles of science and risk (for example, as any entity produced in a certain time, or containing a certain lot of a starting material), and subjected to a disposition decision.

(4) A process consisting of a series of interconnected unit operations or transformations can be considered to be continuous even if it contains transformations of defined quantities of material which might be considered to be composed of a sequence of individual discrete events.

(5) During periods of startup, shutdown or processing of small quantities of material, or both (for example, for development/experimental or clinical studies), it is possible that not all unit operations within a continuous production line will be in normal or steady state conditions at the same time. For example: the first unit operation could already be shut down while the material is processed further in subsequent unit operations. This condition should not automatically invalidate the definition of the process as representative of normal continuous operation; however, care must be taken to understand the impact of this mode of operation on product quality.

3.2.3 *critical process parameter (CPP)*—a process parameter whose variability has a significant impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality (ICH Q8 (R2)).

3.2.4 *critical quality attribute (CQA)*—a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality (ICH Q8 (R2)).

3.2.5 *dynamic or adaptive process control system*—an automated control system that utilizes process and control models and the use of dynamic critical process parameters (CPP) (see Guide E2629 - 11, section 4.2 for detail description) to deliver required product quality. Depending on the dynamics of the process the corrections may be applied immediately as a step change or as a time dependent function (for example, a ramp or exponential function). Such real time control systems may include, for example:

3.2.6 *feedback control*—a control strategy which is intended to eliminate drift or deviation in a specific product attribute away from the target (setpoint) by means of:

(1) Measuring the attributes of material leaving a process operation,

(2) Comparing the measured values with target (setpoint) values for the attributes, and

(3) Using a process model or real-time tuning (that is, reaction to action) in order to calculate revised setpoint values for the relevant process conditions.

3.2.7 *feed forward control*—a control strategy which measures either: (*1*) specific critical attributes of materials as they enter a specific process, or (*2*) other upstream factors (for example, flow rates, temperature, etc.), and uses this information in combination with an appropriate process model to adjust the setpoint of the process conditions in order to reduce the impact of the upstream change on the quality of the material leaving the process step.

3.2.8 *multivariate model based control*—measurements of one or more product attributes and process conditions are used in a model of the process to determine the process conditions required to achieve the desired product quality.

3.2.9 *normal operation*—behavior of the process which can be expected or predicted, or both, based on an understanding of the process. Unforced variability in the process or product which can be expected, predicted and characterized statistically or predictable variability which is forced by an external stimulation, or both, may be considered as normal operation.

3.2.10 *plug flow process*—a process where the residence time distribution (RTD) has zero variability and is equal to the mean residence time.

3.2.10.1 *Discussion*—For example, in an idealized plug flow process, a step change of the quantity, quality, or identity of the input materials is, after a defined time, directly and equally reflected by a step change in the output.

3.2.11 *process control setpoint*—a process control setpoint is a specific target value for a process parameter or product attribute which is used by a dynamic control system. The dynamic process control system will determine what corrective control action to apply in order to try to bring the specific parameter or attribute closer to the setpoint value.

3.2.11.1 *Discussion*—A setpoint may be specified together with upper and lower target values such that corrective control action may be reduced once the value is within the target range. A target range specified by upper and lower target values only has no explicit specified setpoint value and hence corrective process control action is often suspended once the parameter or attribute is within the target range.

3.2.12 *process disturbance*—an un-requested and uncontrolled change in a measured or unmeasured parameter which has the effect of changing the process conditions or product quality (that is, a short-term transient condition).

3.2.13 *process time constant*—a measure of the rate at which the process can change from steady state operation at one condition to steady state operation at another condition.

3.2.14 *quasi-steady state*—conditions where some individual process parameters are consistently varying in time but with a set pattern of variation (for example, compression force in a tablet press) such that the process is in a state of control. In this guide, quasi-steady state conditions are considered equivalent to steady state conditions.

3.2.15 *recipe-based process control system*—an automated control system which maintains specific process parameters at pre-specified fixed values (that is, according to a predetermined recipe) without adjustment of process parameters based on either measurement and feedback of product quality attributes or measurement and feed-forward of input material quality attributes or upstream conditions.

3.2.16 *residence time*—the time that process material is in a specific process environment/vessel/unit operation.

3.2.17 *residence time distribution (RTD)*—a measure of the range of residence times experienced by material passing through a specific process environment/vessel/unit operation.

3.2.17.1 *Discussion*—RTD is impacted by the flow rate of a material. Therefore, if flow rates are changed (for example, due to process or material changes), the RTD will likely change and impact development studies and subsequent commercial manufacturing.

3.2.18 *state of control*—a condition in which the set of controls consistently provides assurance of continued process performance and product quality (ICH Q10).

3.2.18.1 *Discussion*—In CM, the state of control constitutes the manufacture of material with acceptable quality whilst the process variance stays within previously determined ranges, as well as the rejection of identified non-conforming material. State of control should not be confused with just the periods in which the system is producing acceptable material, and atypical process variance should trigger out of trend investigation.

3.2.19 *steady state*—consistent operation over a period of time where all relevant process parameters and product qualities are not subject to significant unforced variation.

3.2.19.1 *Discussion*—Running at a steady state, by itself, does not directly imply that the defined targets are correct with respect to achieving acceptable product quality. Steady state implies only that the process is not subject to significant variance with respect to time. Achieving or maintaining acceptable product quality may require an adjustment of target values and hence a transition between two steady state conditions.

3.2.20 *transient conditions*—conditions where the process is disturbed from steady state or is in transition between one steady state condition to another (that is, the process conditions or product quality are not in steady state or quasi-steady state). Transients may be due to either external disturbances or intentional changes in the selected operating conditions.

3.2.21 *under process control*—behavior of the process when it responds in a predictable way to the actions of the control system and is able to achieve and maintain operation at a specific process control setpoint or setpoints.

4. Significance and Use

4.1 Although some CM is used in the pharmaceutical industry (for example, purified water production), and some processes are inherently continuous individual unit operations (such as dry granulation and compression), these operations are generally operated in isolation and do not deliver the potential benefits of an integrated CM operation. The FDA Guidance for Industry PAT document specifically identifies that the introduction of continuous processing (now redefined as CM) may be one of the outcomes from the adoption of a science-based approach to process design.

4.2 This guide does not:

4.2.1 Suggest that CM is suitable for the manufacture of all pharmaceutical products.

4.2.2 Provide guidance on issues related to the safe operation of a CM process or continuous processing equipment. It is the responsibility of the user of this standard to establish appropriate health and safety practices and determine the applicability of regulatory limitations prior to use.

4.2.3 Recommend particular designs or operating regimes for CM.

4.3 Appendix X1 includes a table comparing the characteristics of continuous and discrete or batch processes.

5. Process Design in Continuous Manufacturing

5.1 *Principles:*

5.1.1 The design of a CM process requires the same good process design and engineering practices (for example compliance to ICH Q8 (R2), Q9, Q10, Q11 or Q13) that may be used in batch process.

5.1.2 However, the design of the CM process may require the consideration of additional factors which are not as important in a batch process.

5.1.3 Hence when designing a CM process, consideration should be given to the process conditions experienced by the materials as they flow through the system, for example:

5.1.3.1 The flow rate, or range of flow rates, through the process (that is, the target plant production rate).

5.1.3.2 The balance between the process and buffer capacities of the elements of the system to ensure that the desired process conditions and overall line flow rates under the required operating regimes can be achieved, for example:

(1) How the capacity of a tablet press is balanced with the feed rate of an upstream powder preparation system,

(2) How the drying capacity of a dryer is balanced with the liquid addition rate of a granulation system, and

(3) Ability to manage heat balance in endo- or exo-thermic reaction operations.

5.1.3.3 The instantaneous/peak flow rate at locations in the system where material flow may be discrete.

5.1.3.4 The flow pattern of the materials in the system (for example, plug flow versus back mixed).

5.1.3.5 The process conditions required in order to achieve a specific transformation.

5.1.3.6 The process time constants, reaction rates, average, maximum and minimum residence times required to achieve a specific process objective.

5.1.3.7 The relationship between material properties, process conditions and equipment design required to achieve a reliable flow of materials.

5.1.3.8 The analysis of the mass and energy balance for the system using process and chemical engineering principles, for example:

(1) Capacity of physical transfer systems, and

(2) Capacity of heating systems.

5.1.3.9 Implementation of appropriate monitoring tools.

5.2 *Process Time Constants:*

5.2.1 The time available for a given process transformation is determined by the residence time of the material in a specific process environment, that is, how quickly material in the process will proceed from initial conditions to final conditions.

5.2.2 As the material flows through the system, rate limiting elements within the process must be considered to ensure that, for a given flow rate, the required process end point or product attribute can be achieved within the time available, for example:

5.2.2.1 A powdered binder may take a given time to react with water in order to become an effective binder. This time may be temperature dependent, and hence, if a powdered binder is to be used, it is important that the relationship between time, temperature and binder hydration is fully understood in order to achieve effective use of the binder as the product flows through the process.

5.2.3 The potential effects on product quality of various time constants of the process and the equipment (for example, effects of thermal mass), especially during start up and transient conditions, should be considered.

5.2.4 An understanding and subsequent verification of the various time constants of the process is specifically important in determining the expected behavior of the process during start up and shutdown and hence the impact on quality decisions regarding the disposition of material manufactured during this period.

5.2.5 Consideration should be given to the use of monitoring systems which ensure that the required product attributes are achieved before the process is allowed to proceed to the next unit operation.

5.2.6 In addition to the time needed to monitor and analyze in process material attributes, considerations should be made for time to identify non-conforming material and to trigger systems to segregate this material.

5.3 *Residence Time, Residence Time Distribution, and the Degree of Back Mixing:*

5.3.1 In order to characterize a continuous process the process residence time and residence time distribution, which is a function of the internal mixing, must be understood and quantified during both start up and normal operation as well as during process disturbance and shutdown conditions (that is, until product is no longer collected).

5.3.2 The flow of product within the system and in particular the degree of back mixing may be characterized using parameters such as RTD, or from appropriate process dynamics models (for example, *n* CSTRs in series or axial dispersion). These can be estimated by an appropriate combination of:

5.3.2.1 Process modeling,

5.3.2.2 Characterization tests using specific markers/tracers, and

5.3.2.3 Online/inline process measurement of appropriate product attributes.

5.3.3 Two extremes of mixing are commonly identified as "plug flow" or "fully back mixed," but most processes will have some attributes of both, and hence are referred to as having a 'degree of back mixing.'

5.3.4 An estimation of the RTD within the process enables an understanding of the following:

5.3.4.1 Which output material contains which input material,

5.3.4.2 Which process conditions have had an impact on a specific quantity of output material,

5.3.4.3 How minor and transient changes in feed or process conditions will impact output product attributes, and

5.3.4.4 The degree of intermixing with adjacent material during the transition through the process equipment.

5.3.5 Process understanding and risk analysis should be used to demonstrate that both product quality and the ability to identify specified quantities of material at specified locations within the process is not adversely impacted by the degree of back mixing under:

5.3.5.1 Initial startup conditions;

5.3.5.2 Normal operating conditions, where the process is in a state of control;

Discussion—Normal operation in a state of control does not necessarily imply steady state, but does imply the process variance is typical (within trend).

5.3.5.3 Disturbances and abnormal operating conditions; and

5.3.5.4 Shutdown conditions.

5.3.6 In particular, an understanding and quantification of the residence time distribution may be used to determine which material may have been affected by a deviation in process conditions and hence the specific identity of any product within the scope of any investigation or disposition decision.

5.4 *Product Transport and Material Properties:*

5.4.1 A CM process may consist of a number of unit operations (a single step in the process intended to transform a material from one condition to another, for example, powder to granule, wet to dry) linked together by elements which transport materials between sequential unit operations.

5.4.2 Careful consideration should be given to the design of transport and flow control elements within a continuous system in order to ensure that materials will flow in a predictable way without adverse impact on product quality (for example, segregation, sedimentation, and phase separation during transport).

5.4.3 Transporting and controlling the flow rate of cohesive powders may be a specific problem in this respect. Hence, the handling and flow properties of materials to be processed should be determined as early as possible within the development of the product such that the process equipment may be designed appropriately.

5.4.4 Characterization of materials using laboratory techniques on small samples may give good early indication of potential problems but where there are concerns about material properties it is recommended that testing of representative equipment and representative materials is carried out under representative process conditions as early as possible.

5.4.5 Transport processes may also cause some degree of transformation (for example, segregation or attrition of powders) and therefore careful consideration should be given to ensure:

5.4.5.1 Effects are identified and understood,

5.4.5.2 Steps are taken to minimize such effects during plant design, and

5.4.5.3 Controls are put in place to manage or mitigate such effects over the entire range of operating conditions.

6. Operation of Continuous Manufacturing Systems

6.1 *Operational Considerations:*

6.1.1 In order to successfully introduce continuous processing, due consideration should first be given to the overall operation and support of the system during the lifecycle of the plant and product, for example:

6.1.1.1 Considerations for process and product development based on business needs:

(1) Flexibility of the system to produce small quantities of material under different operating conditions during development of product and process understanding, and

(2) Suitability for manufacture of variable quantities of product at stable operating conditions for clinical trials supplies.

6.1.1.2 Considerations for increasing process capacity from development to commercial production:

(1) Scale up of run length or duration,

(2) Scale out by addition of parallel processing lines,

(3) Increase in production rate,

(4) Increase in size of equipment, and

(5) Scale-up effects on critical process parameters.

6.1.1.3 For stable manufacturing operations over the target run length, consider:

(1) Ability of the system to produce consistent product over the intended duration of the operation,

(2) Mechanisms of failure and degradation of performance together with robust methods of detection,

(3) Degree of redundancy in equipment and sensors required to assure continuous stable operation, and

(4) Necessity and frequency for operator intervention in order to maintain normal operation.

6.1.1.4 In addition, sites conducting CM, particularly those that have not previously operated CM, should consider:

(1) Training of development, manufacturing and quality assurance personnel, both existing and new hires, in the theoretical and practical aspects of continuous processing, and

(2) Impact of continuous operation on facilities, staff and systems (for example, extended shift working patterns, deviation management).

This list is not intended to be exhaustive, but points to major aspects of the pharmaceutical quality system, noted in ICH Q10.

6.2 *Operating States:*

6.2.1 The operation of a CM system must be considered over the whole life cycle of the product (that is, development, validation, clinical trial supply, technology transfer, commercial manufacturing, and product discontinuation) for which it is intended to be used.

6.2.2 Risk analysis techniques, practical tests, or modeling tools, or any appropriate combination of these, should be employed to ensure that all potential impacts on product quality are understood and appropriately managed over all potential operating states, for example:

6.2.2.1 Equipment start-up (for example, initialization and warm up ready for processing);

6.2.2.2 Process start-up (introduction of feed materials to start processing and reaching state of control, that is, the process to manufacturing material of acceptable quality and with typical process variance);

6.2.2.3 Normal, steady state, and in specification operation (that is, verified to deliver material which is suitable to be released);

6.2.2.4 Transient operation during rate or product specification changes;

6.2.2.5 Replenishment of feedstock materials; and considering the impact of any variability in raw materials;

6.2.2.6 Process pause or hold (for example, as a result of alarm conditions);

6.2.2.7 Process shutdown (including extracting product that meets specification);

6.2.2.8 Emptying of equipment of any residual material that does not or would not meet specification;

6.2.2.9 Cleaning/ product/ grade changeover;

6.2.2.10 Controlled safe status (software-controlled safe status (SSS), hardware-controlled safe status (HSS)); and

6.2.2.11 Mechanically shut down and out of service.

In some defined circumstances, manufacturers of drug substance or drug product, or both, may reprocess, or continue to process material held under quarantine, provided the requirements for rework/reclaim of the production material are defined in a written procedure and the rework/reclaim is approved by the quality authority, and when other appropriate considerations are met, that is, is part of system design (for example, impact on system dynamics/residence time distribution, batch/material traceability, strategy for material diversion, etc. are established).

6.3 *Process Robustness:*

6.3.1 CM may pose challenges due to behaviors of both equipment and material which occur gradually over a long period and which therefore may not be easily observed during either batch processing or short test runs of continuous systems.

6.3.2 Suitable risk analysis, practical tests and modeling techniques should be considered in order to determine and evaluate potential challenges in maintaining stable process conditions during the operation of CM over the full length of the required production run, and any sampling or data review as part of this risk analysis and on-going risk management should be done in consideration of the on-going process dynamics.

6.3.3 Consideration should be given to:

6.3.3.1 The potential for undesirable buildup of material due to physical and chemical processes, for example:

(1) Equipment surfaces (for example, impact on heat transfer);

(2) Ducts and pipes (for example, impact on flow patterns);

(3) Instruments and probes (for example, impact on accuracy, etc.);

(4) Filters (for example, impact on flow and pressure of fluids);

(5) By-products with different or undesirable characteristics, or both; and

(6) Crystallization and encrustation.

6.3.3.2 Changes in raw material behavior between batches/ sources/suppliers which may not be covered within existing quality control requirements, for example:

(1) Flow properties,

(2) Electrostatic properties, and

(3) Safety properties.

6.3.3.3 Impact of environmental changes on raw material and product, for example:

(1) Temperature, and

(2) Relative humidity (RH).

6.3.3.4 Changes in plant and equipment characteristics over time and with prolonged uninterrupted use, for example:

(1) Changes in surface finish, and

(2) Changes in clearances due to wear.

6.3.4 The maximum length of time over which the process is run may be determined by monitoring specific product attributes or process parameters rather than by validating a single fixed length of run time.

6.3.5 Where one unit operation within a process line is determined to be disproportionally vulnerable to degradation in performance or lack of robustness then strategies to maximize the potential run time in order to avoid the need to stop the overall process should be considered, for example:

6.3.5.1 Rapid change over of individual items of equipment, and

6.3.5.2 Redundancy, parallelization, or duplication of critical equipment elements (for example, filters, pumps, tubing, critical instruments).

6.4 *Requirement for Operator Intervention:*

6.4.1 Generally, CM should be expected to operate with the minimum practical level of operator intervention.

6.4.2 Processes should be developed so as to not require operator intervention. Due to the time-scale of material movement and attribute monitoring, automated actions are preferable and advantageous.

6.4.3 When operator intervention is required to maintain stable process operation, the frequency should be minimized or process redesign considered.

6.4.4 Unplanned operator intervention should be considered as a potential source of uncontrolled variability. Continued unplanned intervention may indicate a lack of process robustness or uncontrolled or unmanaged variability in process conditions or material properties.

6.4.5 Continuous improvement tools (for example, real time statistical process control) should be used during operation in order to identify the causes of any unplanned operator intervention and appropriate actions should be taken to ensure that any impact on product quality is fully understood and that the root cause of the need for intervention is eliminated and monitored to ensure the adequacy of the correction.

7. Product Quality Control for Continuous Manufacturing

7.1 CM provides several potential opportunities to improve control of product quality and to increase flexibility of manufacturing.

7.2 *Batch Definition for Continuous Manufacturing:*

7.2.1 The designation of batch size is proposed and justified by the manufacturer, considering the control strategy and risk to the patient. The definition of a batch has regulatory implications, particularly with respect to GMPs, product recalls, and other regulatory decisions. Current GMP regulations describe a ‘batch’ as a specific quantity of drug or other material that is intended to have uniform character and quality within specified limits and is produced according to a single manufacturing order during the same cycle of manufacture. The batch size can be defined based on the production period, quantity of material processed, quantity of material produced or production variation (for example, different lots of incoming raw material).

7.2.2 In a CM process, the amount of material in a batch for release could be defined as:

7.2.2.1 All of the material discharged from the process between two specific times (irrespective of the amount of material produced).

7.2.2.2 A specific quantity of material produced (irrespective of the time taken).

7.2.2.3 All of the material produced between two specific process events (for example, specific process conditions).

7.2.2.4 All of the material that is intended to contain a specific lot or quantity of a specified input material.

7.3 *Control Strategy:*

7.3.1 A comprehensive control strategy for CM may include additional elements such as input material control, in-process attribute measurement, material diversion, etc. in order to ensure the process stays in a state of control. Control strategy implementations can be categorized into three levels.[5]

7.3.2 The dynamic nature of continuous manufacturing systems promotes the adoption of dynamic process control, although a hybrid approach combining the different levels of control is viable for some CM process designs.

7.3.2.1 Level 1: Quality assurance via application of dynamic or adaptive process control system.

(1) CM provides a potential opportunity to use a dynamic or adaptive process control system to monitor and control the quality attributes of materials in real-time.

(2) In dynamic or adaptive process control, system process parameters are monitored and may be adjusted in response to disturbances to ensure that the quality attributes consistently conform to the established acceptance criteria. Timely monitoring of in process material attributes with process analytical technology (PAT) (using on-line, at-line or predictions of material attributes from process models) can be used to adjust the process.

(3) The successful application of a dynamic or adaptive process control system requires a high degree of product and process understanding as the design of an engineering control system entails expressing the dynamic relationships among process parameters, raw material and product attributes in a quantitative and predictive manner.

(4) The ability of a dynamic or adaptive process control system to compensate for variation in the raw material attributes or external disturbances to the process conditions significantly reduces the risk of producing out of specification material and hence the requirement for routine segregation / diversion of out-of-specification is also reduced.

(5) Statistical monitoring tools, for example, univariate or multivariate statistical process control, may be used to demonstrate that the dynamic or adaptive process control system is ensuring that the process is operating in a state of control where there is a very low probability of out of specification material being produced. Successful implementation of a dynamic or adaptive process control system can support a real-time release strategy.

(6) This high impact model should be supported by a verification approach that may include extensive side-by-side testing of the model and reference method for commercial batches until a full range of variability is experienced. Robust correlation is essential for these models, and subsequently lifecycle verifications should occur.

7.3.2.2 Level 2: Quality assurance via operation within an established design space verified by in-process material testing and confirmatory end product testing.

(1) The product and process understanding obtained through the establishment of a multivariate design space facilitates the identification of potential sources of raw material and process variability that can impact product quality.

(2) Understanding the impact that variability from these sources has on in-process materials, downstream processing, and drug product quality provides an opportunity to shift controls upstream and to reduce the reliance on end-product testing.

(3) Product quality may be assured by a combination of operating within an established design space verified using in process testing (on-line, at-line or predictions of material attributes from process models) and confirmed by end product testing.

7.3.2.3 Level 3: Quality assurance via operation within validated and constrained material attributes and process parameters and release supported by in-process and end product testing.

(1) Quality assurance via operation control relies on tightly constrained material attributes and process parameters.

(2) The risk of releasing poor quality product is mitigated through extensive and statistically adequate in-process and end-product testing, at a frequency appropriate for the process dynamics (intermixing) and process variability. Timely measurement of in process material attributes is necessary.

(3) There may be limited understanding on how raw material and process variability affects product quality. Variability of raw material attributes (some of which may be poorly characterized or understood, or both) and the risk of potential transient process disturbances makes operating a CM process within very tightly constrained process parameter limits potentially challenging, with potential for a high occurrence of out of specification material requiring segregation / diversion in real time.

(4) In order to justify this level of control strategy, the process must be demonstrated to be appropriately stable and capable of delivering a consistent output (for example by the introduction of large back mixed buffers), and may generally not be viable without considerable process history.

7.4 *Quality Decisions:*

7.4.1 Decisions on the quality of product manufactured by a CM system should be guided by a clear understanding of the state of the control of the system.

7.4.2 *State of Control:*

7.4.2.1 State of control is a condition in which a set of controls consistently provides assurance of continued process performance and product quality. A CM process operating within a state of control helps to ensure that product with the

[5] "Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Production," *Journal of Pharmaceutical Innovation*, Vol 10, Issue 3, Sept 2015.