Designation: E2968 – 14

Standard Guide for Application of Continuous Processing 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 continuous processing technologies for the manufacture of pharmaceutical products.

1.2 Particular consideration is given to the development and application of the appropriate scientific understanding and engineering principles that differentiate continuous manufacture 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 in 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 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 a new process, or the improvement/redesign of an existing one.

1.5 The values stated in SI units are to be regarded as standard. 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 and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

E2475 Guide for Process Understanding Related to Pharmaceutical Manufacture and Control

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

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

2.2 *FDA Documents:*[3]

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

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) which is non zero and potentially significant compared to the mean residence time.

3.2.1.1 *Discussion*—For example, in an idealized 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 equipment characteristics, residence volume,

[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 E55.01 on Process Understanding and PAT System Management, Implementation and Practice.

Current edition approved Dec. 1, 2014. Published April 2015. DOI: 10.1520/E2968-14.

[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.

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).

3.2.2 *controlled state*—A process is in a controlled state when it is: (*1*) Under Process Control, and (*2*) operating normally, such that the measured critical quality attributes of the product are within the defined acceptable range.

3.2.3 *dynamic process control system*—an automated control system which monitors the condition of the product or the process, or both, predicts or detects a change to the product quality away from a target condition (that is, Setpoint), and then changes the process conditions during processing in order to maintain the product quality at the target value (or within the specified range of target values). 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:

3.2.3.1 *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 containing appropriate process dynamics in order to calculate revised Setpoint values for the relevant process conditions.

3.2.3.2 *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.

3.2.3.3 *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 correct product quality.

3.2.4 *continuous process*—a process where, during normal operation, raw materials are continuously fed into the system at the same time as acceptable product is continuously removed from the system.

3.2.4.1 *Discussion*—(*1*) In a continuous 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 continuous process may be operated to transform a pre-defined quantity of material into a pre-defined physical quantity of product which is then subjected to a disposition decision. The size of the resulting lot is predefined by the amount of starting material (with the option to divert certain amount of material taken from online control), and this is comparable to conventional discrete or batch manufacturing operations.

(*3*) Alternatively a continuous process may be operated with an 'infinite' 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 also contains transformations of defined quantities of material which, when viewed at a particular scale of scrutiny or level of detail, 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.

3.2.5 *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, or both, which is forced by an external stimulation may be considered as normal operation.

3.2.6 *plug flow process*—a process with a residence time distribution (RTD) which approaches zero.

3.2.6.1 *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.

3.2.7 *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.

3.2.7.1 *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.

3.2.8 *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).

3.2.9 *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.

3.2.10 *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). In this guide, quasi-steady state conditions are considered equivalent to steady state conditions.

3.2.11 *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.

3.2.12 *steady state*—consistent operation over a period of time where all relevant process parameters and product qualities are not subject to variation outside of a defined range of values.

3.2.12.1 *Discussion*—(*1*) A steady state condition by itself does not directly imply that the defined targets are correct with respect to achieving acceptable product quality.

(*2*) Steady state implies only that the process is not subject to significant variance with respect to time.

(*3*) Achieving or maintaining acceptable product quality may require an adjustment of target values and hence a transition between two steady state conditions.

3.2.13 *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.

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

3.2.15 *residence time distribution (RTD)*—a measure of the range of residence times experienced by material passing through a specific process environment/vessel/unit operation. Hence in a process where the RTD is not zero a quantity of material which all enters the process at the same time may leave at different times and hence is not all resident in the process for the same time. The RTD can be used to characterize this difference in residence time and hence understand how changes to the process or materials will propagate through the process.

3.2.16 *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.

3.2.16.1 *Discussion*—Physical or chemical limitations may prevent a process from responding to the process control system (for example, control valve already wide open) and hence under such conditions the process might be considered to be not fully Under Process Control. In such a situation (for example, transient conditions, start up and shutdown), the plant may be considered to be Under Process Control if the Process Control Setpoints are managed such that the process is not constantly operated at its limits.

4. Significance and Use

4.1 Although some continuous processing is used in the pharmaceutical industry (for example, purified water production, 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 continuous manufacturing operation. The FDA Guidance for Industry PAT document specifically identifies that the introduction of continuous processing 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 continuous production is suitable for the manufacture of all pharmaceutical products.

4.2.2 Provide guidance on issues related to the safe operation of a continuous 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 continuous manufacturing.

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

5. Operation of Continuous Manufacturing Systems

5.1 *Operational Considerations:*

5.1.1 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:

5.1.1.1 Considerations for process and product development:

(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.

5.1.1.2 For increasing process capacity from development to commercial production, consider:

(1) Scale up of run length duration,

(2) Increase in production rate,

(3) Scale out by addition of parallel processing lines, and

(4) A risk based approach to scale up of continuous process.

5.1.1.3 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.

5.1.1.4 In addition, where a site has not previously operated, a continuous process consideration should also be given to:

(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).

5.2 *Operating States:*

5.2.1 The operation of a continuous process 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.

5.2.2 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:

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

5.2.2.2 Process start-up (introduction of feed materials to start processing and reaching steady state);

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

5.2.2.4 Transient operation during rate or product specification changes;

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

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

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

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

5.2.2.9 Cleaning/ product/ grade changeover

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

5.2.2.11 Mechanically shut down and out of service.

5.3 *Process Robustness:*

5.3.1 Continuous processing 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.

5.3.2 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 a continuous process over the full length of the required production run.

5.3.3 Consideration should be given to:

5.3.3.1 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.

5.3.3.2 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.

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

(1) Temperature, and

(2) Relative humidity (RH).

5.3.3.4 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.

5.3.4 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.

5.3.5 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:

5.3.5.1 Rapid change over of individual items of equipment, and

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

5.4 *Requirement for Operator Intervention:*

5.4.1 Generally, a continuous process should be expected to operate with the minimum practical level of operator intervention.

5.4.2 The necessity and frequency for operator intervention in order to maintain stable process operation should be minimized, and prevented if possible.

5.4.3 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.

5.4.4 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.

6. Process Design in Continuous Production Systems

6.1 *Principles:*

6.1.1 The design of a continuous process requires the same good process design and engineering practices used in a traditional batch process.

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

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

6.1.3.1 The overall flow rate through the process (that is, the target plant production rate).

6.1.3.2 The balance between the process capacity of each element 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 processing 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.

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

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

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

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

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

6.1.3.8 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.

6.1.3.9 Appropriate monitoring tools are implemented.

6.2 *Process Time Constants:*

6.2.1 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.

6.2.2 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:

6.2.2.1 A powdered binder may take a given time to react with water in order to become an effective binder,

6.2.2.2 This time may be temperature dependent, and

6.2.2.3 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.

6.2.3 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.

6.2.4 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.

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

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

6.3.1 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).

6.3.2 The flow of product within the system and in particular the degree of back mixing may be characterized using parameters such as Residence Time Distribution (RTD), or Péclet number and should be estimated by an appropriate combination of:

6.3.2.1 Calculation and process modeling,

6.3.2.2 Validation tests using specific markers/tracers, and

6.3.2.3 Online process measurement of appropriate product attributes.

6.3.3 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.'

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

6.3.4.1 Which output material contains which input material,

6.3.4.2 What process conditions have had an impact on a specific quantity of output material,

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

6.3.4.4 The degree of recycle.

6.3.5 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:

6.3.5.1 Initial startup conditions;

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

Discussion—Normal operation in a state of control does not necessarily imply steady state

6.3.5.3 Disturbances and abnormal operating conditions; and

6.3.5.4 Shutdown conditions.

6.3.6 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.

6.4 *Product Transport and Material Properties:*

6.4.1 A continuous 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.

6.4.2 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).

6.4.3 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.

6.4.4 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 as early as possible.

6.4.5 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:

6.4.5.1 Effects are identified and understood,

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

6.4.5.3 Controls are put in place to manage or mitigate such effects during operation.

7. Product Quality Control for Continuous Processes

7.1 Continuous processes provide an opportunity to monitor and control the critical parameters of the process and the critical quality attributes of materials in real time as materials flow through the system.

7.2 The application of Guides E2537 and E2898 should be considered.

7.3 Risk assessment and process understanding should be employed to determine the degree and type of monitoring and process control required to produce material within specification and should take account of the feasibility of implementing reliable control action.

7.4 A real time flow of process and product information from a well-designed continuous process provides an opportunity to gather more information from smaller quantities of product and hence build a higher level of process understanding in a shorter time and at lower cost.

7.5 *Sampling and Data Collection within a Continuous Process:*

7.5.1 When developing and verifying measurements which will be used to monitor and control a continuous process, the representativeness of the measurement and the timeliness of resulting information should be considered in both time and space, for example,

7.5.1.1 The intended scale of scrutiny of the sampling and measurement system.

7.5.1.2 How is the measurement impacted by the flow of product within the process?

7.5.1.3 How representative is this measurement of the whole process stream?

7.5.1.4 The impact of process dynamics on the requirement of the sampling and measurement system, that is, how fast can the process and, hence, the quality attribute or process parameter change?

7.5.1.5 The impact of process dynamics and process control requirements, that is, how rapidly can useful information be derived from the measurement relative to the dynamics of the process and how rapidly can effective corrective action be taken?

7.5.2 In order to ensure that a process parameter or product attribute cannot move outside the validated process window, or acceptable range, without being detected, it is important to ensure that the control and monitoring system is able to take measurements at a frequency which is appropriate to the dynamic response time of the parameter or attribute.

7.5.3 Due consideration should be given to how to handle measurement noise due to variability in sample presentation which is potentially greater in an online system compared to an at-line or offline system, where the sample presentation etc. may be better controlled.

7.5.4 Specific consideration should be given to:

7.5.4.1 The tradeoff between measurement quality and measurement frequency,

7.5.4.2 The use of filtering to remove signal noise,

7.5.4.3 The impact of filtering on dynamic response of the measurement (that is, loss of dynamic response),

7.5.4.4 The use of suitable signal processing or statistical techniques in order to extract meaningful process information from background noise, and

7.5.4.5 Strategies for avoiding excessive control action in response to normal process variability.

ROBUSTNESS OF INSTRUMENTS AND ANALYZERS

7.6 *Information Used for Product or Process Control May be Derived From:*

7.6.1 Direct measurements of CPPs (that is, typical instruments such as temperature pressure and flow).

7.6.2 Direct measurements of CQAs via suitable online analytical technology, for example,

7.6.2.1 Spectroscopic analysis for composition

7.6.2.2 Image analysis, laser diffraction, electro-acoustic analysis for particle size distribution (PSD)