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# Standard Guide for Application of Continuous Processing in the Pharmaceutical Industry[1]

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## 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,

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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.

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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 un-controlled 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)

7.6.3 Predicted values for a CQA using a combination of one or more CPP(s) in a validated model. This may be particularly useful where a CQA may not be measured directly during the process.

7.7 In all cases, it is essential that the primary sensors are robust, reliable and accurate over the expected run time of the process and likely range of the parameter to be measured. Specific consideration should be given to:

7.7.1 The long term effects of fouling and buildup of product on a sensor;

7.7.2 The effects of changes in environmental conditions over the life of the process and the sensor;

7.7.3 Requirements for cleaning, recalibration, or maintenance in order to maintain sensor performance over the expected duration of the process;

7.7.4 The impact on the process and quality control strategy of short periods of planned or unplanned maintenance of a sensor;

7.7.5 The impact on the process of the complete failure of the sensor;

7.7.6 The requirement for duplicate or redundant sensors;

7.7.7 The potential to use information from alternative sources of data (that is, surrogate measurements) to enable the operation of the process in the event of failure or maintenance of the sensor;

7.7.8 The strategy for reconciling potentially different values from duplicate, redundant sensors, or alternative sources of data; and

7.7.9 Strategy for maintenance of any models used to predict CQAs.

7.8 *Use of Surrogate Measurements:*

7.8.1 When the direct measurement of specific process parameters or material attributes cannot be made then surrogate measurements of the product or process which can be taken at a higher frequency and used in conjunction with suitable models may be considered.

7.8.2 In using a surrogate measurement specific consideration should be given to:

7.8.2.1 the degree of correlation between the surrogate and the direct measurement

7.8.2.2 The range of process conditions or operating time over which the surrogate measurement has been validated to confirm that the process has remained within acceptable limits

7.8.2.3 The setting of warnings/ alarms/ control actions to be used in conjunction with a surrogate measurement to indicate that the process has not operated normally

7.8.2.4 The strategy for reconciling potentially different values for the same parameter or attribute when measured or calculated from alternative sensors or sources of data

## MATERIAL IDENTIFICATION AND TRACEABILITY

7.9 *Principles:*

7.9.1 For any specific quantity of product produced from a continuous processing system and released to the market it must be possible to identify the lots of raw materials from which it has been manufactured and reliably link the relevant process information to it in a timely manner.

7.9.2 This requires a demonstrated ability to:

7.9.2.1 Identify specific quantities of raw material, intermediate or final product, or both.

7.9.2.2 Record when and where specific quantities of particular lots of raw materials entered the process.

7.9.2.3 Record where and when specific quantities of particular lots of materials exit from the process.

7.9.2.4 Understand and predict how the flow patterns (for example, residence time and residence time distribution) at different flow rates and operating conditions may impact material flow within the system, especially within the limits material is collected for release. Material flow can be described as full residence time distributions or limits thereof. The goal should be to identify the potential impact of a sudden change of input material attributes on the continuous output and to correlate the relevant process data (from all unit operations) to the product collected.

7.9.2.5 Understand and predict how the dynamic behavior of the process (for example, process time constant) at different and varying flow rates or operating conditions, or both, may impact material flow within the system, especially within the limits material is collected for release.

7.9.2.6 Understand the overall flow of product in the system or subsections of the system (that is, mass balance) and the ability to account for material which may be:

*(1)* Removed deliberately from the system for sampling;

*(2)* Unintentionally lost from the system due unforeseen events;

*(3)* Retained in the system, for example, in the form of stable surface coatings;

*(4)* Held up in the system and subsequently released on a controlled basis, for example, material held on filters and subsequently released on filter blowback;

*(5)* Held up in the system and subsequently released on an uncontrolled basis, for example, hang ups in vessels, etc.; and

*(6)* Removed from the system but subsequently determined as being of suitable quality and re introduced to the system for processing.

7.9.2.7 Demonstrate an appropriately reliably and timely link between relevant product quality information (for example, values of CPPs and CQAs) and any specifically identified product, taking into account all of the above considerations.

7.9.2.8 Understand and account for the effect of differing lots of raw material on calibration models.

## QUALITY DECISIONS

7.10 *In a Continuous Process the Amount of Material Subject to a Quality Disposition Decision Could be Defined As:*

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

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

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

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

7.11 Continuous processing systems may be designed such that a portion of in-process material or final product that does not meet quality requirements is diverted to quarantine or waste.

7.12 As a consequence it is possible that not all of the materials that were originally fed into the process, as part of the original single manufacturing order, will be in the finished product intended for release to the market.

7.13 Regulations may define the quantity of product for release to the market (that is, 'batch') in a way which may impact on the approach taken to segregate good product from out of specification material.

7.14 Hence where the diversion/separation of material which does not meet quality requirements is employed as part of the product quality control strategy then this must be carefully assessed and may need to be justified to the appropriate regulatory authority.

7.15 Diversion/acceptance criteria must be suitable to ensure compliance of the entirety of the material subjected to the release decision ("good material") to the applicable specifications.

7.16 Real time diversion/rejection of material which does not meet acceptance criteria must be justified by proper demonstration that the diversion/rejection decisions are based on reliable data and proper understanding of process dynamics.

7.17 However, excessive rejection of material may indicate that the underlying process is not robust or is not operating normally, or both.

7.18 Appropriate process engineering, modeling, testing and risk assessment may be required in order to ensure that the principles behind the following elements are well understood:

7.18.1 How unique identities will be assigned to quantities of final product leaving the process, including.

7.18.2 What specific quantity of final product will be given a unique identity, including for example:

7.18.2.1 Consideration of the risks associated with producing large quantities of product over a long production run, and

7.18.2.2 Products that may contain multiple lots of input materials.

7.18.3 How raw materials will be identified as they are fed into the process.

7.18.4 How the raw materials will become distributed within the process stream.

7.18.5 Which identified quantities of final product contain which quantities of identified raw material.

7.18.6 How raw material will be transformed within the process and hence what process conditions have been used in the production of specifically identified quantities of final product.

7.18.7 How materials subject to any unexpected or adverse processing conditions will be distributed within the process and hence which identified quantities of product may contain non-representative material.

7.18.8 The extent and acceptability of any intentional or unintentional recycling or back mixing within the process, hence, which identified quantities of final product, may contain older or retained material.

7.18.9 The sampling requirements required in order to give an acceptable degree of assurance that the quantity of material is homogeneous when taking into account variability in both space and time.

7.18.10 How conforming material and non-conforming material will be detected and differentiated.

7.18.11 The implication, with regard to the robustness of the process effectiveness of the process control system, of both frequency and extent of any diversion of non-conforming material during start up and normal operation.

## 8. Process Control Systems for Continuous Production

### DESIGN

8.1 *Design Objective:*

8.1.1 The design of the process control for a continuous process should consider the following objectives:

8.1.1.1 Ensuring that all material released from the process can be demonstrated to be within the required specification limits.

8.1.1.2 Reducing variability within the acceptable specification limits by automatically taking appropriate actions in a timely manner to adjust process parameters within a validated range such that the product quality is maintained closer to a specified target or set point.

8.1.1.3 Maximizing productivity and minimizing waste.

8.2 *Design Principles:*

8.2.1 Objective (8.1.1.1) may be realized by an automated recipe-based control system with appropriate sampling, testing, quality control procedures, and equipment mechanisms to detect and reject materials which are out of specification. Objectives (8.1.1.2) and (8.1.1.3) are generally more likely to be achieved by a dynamic process control system; however, the application of such a system relies on:

8.2.1.1 Reliable online measurement of CQA values.

8.2.1.2 Ensuring that the impact of any changes to the CPP values on the product quality is fully understood and can be predicted.

*(1) For Example*—This might be demonstrated by means of a process model which has been validated against a suitable combination and range of changes to CPP values which the control system would be allowed to make.

8.2.1.3 Suitable methods to ensure that the range and rate of adjustment of the CPP are appropriate to the current condition of the process.

*(1) For Example*—It may be appropriate to limit the allowable range/rate over which CPPs may be adjusted by application of simple fixed limit values. However where there is the potential for significant interactions between the effects of CPPs then it may be that limits and rate of change for one CPP is calculated based on other CPPs and CQAs.

8.2.2 The effectiveness of a particular control strategy and the requirement for dynamic control action can be determined by using suitable statistical tools, for example, Statistical Process Control (SPC) that may be used in real time to:

8.2.2.1 Determine the robustness of the process and normal variability of product quality achievable by the process.

8.2.2.2 Quantify the normal capability of the process to consistently produce good quality product.

8.2.2.3 Identify disturbances which might lead to the production of out of specification material if no positive control action is taken.

8.2.2.4 Identify the improvements in process robustness and capability due to the application of dynamic control action.

8.3 *Design Considerations:*

8.3.1 The design of a control system for a continuous process should be considered in terms of:

8.3.1.1 Ease of initial development and validation.

8.3.1.2 Potential to demonstrate improvement in product quality.

8.3.1.3 Availability of suitably accurate and reliable sensors.

8.3.1.4 Ability to develop suitable control strategies which can respond predictably to sources of variability (including variability in attributes of materials which affect the process but are currently not routinely measured).

8.3.1.5 Risk associated with permanent or transient sensor failure.

8.3.1.6 Requirements for redundancy or internal continuous verification, or both.

8.3.1.7 Process dynamics and product CQAs.

8.3.1.8 The ability to display in real-time and record quality data for the product and the process (ideally in the form of control charts or an equivalent).

8.3.2 For dynamic control systems the following configurations should be considered:

8.3.2.1 Feedback control.

8.3.2.2 Feed forward control.

8.3.2.3 Multivariate model-based control.

8.3.3 Note that:

8.3.3.1 Typical systems may combine any or all of these techniques.

8.3.3.2 Care must be taken when using model based systems to consider the range of process conditions for which process models are valid or responses to control changes are linear, or both.

8.3.3.3 In all cases, the rate at which corrective actions are applied to the process must take account of the dynamic behaviors of the process. Failure to do this may result in a situation of "over control" which may result in an increase in variability as a result of excessive control action.

**CONTROL SYSTEM ROBUSTNESS**

8.4 *Operating Considerations:*

8.4.1 Consideration should be given to how the control system may operate during extended production runs where individual elements (for example, online analyzers) may require routine attention (for example, for cleaning). Strategies employed can include:

8.4.1.1 Online cleaning of instruments and analyzers.

8.4.1.2 Providing a second, duplicate analyzer.

8.4.1.3 Measuring and controlling the process using simple uni-variate measurements for short periods using the most recent process parameters or information derived from the online analyzer.

8.4.1.4 Stopping production or diverting and tagging material as non-releasable material until subject to offline analysis (for example, if normally reliant on a single online analyzer that is temporarily offline).

8.5 *Design for Robustness:*

8.5.1 Good process engineering practices (for example, time or frequency domain analysis) should be employed to ensure that:

8.5.1.1 Over control, unstable, or oscillatory behavior is avoided.

8.5.1.2 The system response to changes in measured variables or process set point is acceptable.

8.5.1.3 The system response in reducing or eliminating persistent/constant offsets from target or set point is acceptable.

8.5.1.4 The system response during start up and shutdown is acceptable.

8.5.1.5 The system response during transitions between any manual intervention and automatic control is acceptable.

8.5.2 Additionally, in situ testing of the system should be considered to verify proper system response and the achievement of design criteria.

## 9. Development of Continuous Processes

9.1 The development of a continuous process should follow established principles and good practices which are applied to all pharmaceutical process development projects. Additional consideration should be given to the following:

**PARAMETER SCREENING**

9.2 The effects of changes to process parameters and raw material attributes on product attributes may be investigated by:

*(1)* Starting the process and setting initial process parameters.

*(2)* Holding that parameter at a steady value for a time determined by the dynamic behavior of the process to be sufficient to ensure that the process is operating in a steady condition and that both product and information collected is representative of the selected operating conditions.

*(3)* Collecting product or information about the process.

*(4)* Setting a new set of process parameters during the operation of the process and repeating the cycle 1–3 above with the new parameter values.

9.3 Both theoretical analysis and practical testing with representative materials may be used to identify the process parameters and determine ranges of values to be investigated in further studies.

9.4 Investigations should be conducted using a structured approach which is statistically valid.

9.5 Where individual process steps or unit operations are developed in isolation, the potential interaction between individual steps should be considered when they are integrated into a fully continuous process. In particular, a unit operation/

process step that creates acceptable material in isolation could be unsuitable for extended operation in a fully integrated process line.

### DETERMINATION OF PROCESS DYNAMICS

9.6 The process dynamics, that is, rate and sensitivity, should be understood by considering:

9.6.1 Desirable and undesirable transformations together with associated rate-determining factors;

9.6.2 Residence times, flow rates, and mixing and residence time distributions of material;

9.6.3 Impact of changes in raw materials attributes;

9.6.4 Sensitivity and dynamic response of CPPs to changes in set point,

9.6.5 Sensitivity and dynamic response of CQAs to changes in CPPs;

9.6.6 Scale of scrutiny and representativeness of process measurement and monitoring;

9.6.7 Accuracy, stability, and sampling rate of online analyzers or process models, or both;

9.6.8 Process time constants, control system response, and stability criteria; and

9.6.9 Quality control of material manufactured under startup and shutdown conditions

9.7 The impact of changes in the process production rate or equipment scale changes, or both, on the process dynamics should also be considered.

### PROCESS VALIDATION AND VERIFICATION

9.8 FDA Guidance for Industry PAT and Guide E2537 should be consulted for guidelines for process verification. Guide E2898 should be consulted for the validation of PAT applications.

9.9 In verifying the ability of a continuous processing system to achieve a state of control and deliver the specified performance and reproducibility the following should be considered:

9.9.1 The process conditions which define the end of start up and the start of normal production conditions under which material be collected for later release (that is, product quality within acceptable limits).

9.9.2 The ability of the process to reach and detect the start of normal production in a state of control (that is, an acceptable steady state operation without frequent excursions outside of acceptable limits).

9.9.3 The ability of the system to maintain the intended process conditions over the intended life of the process.

9.9.4 The ability of the system to detect excursions from the target CPP or CQA values and use a sufficient understanding of process dynamics in order to:

9.9.4.1 Divert to waste any identified non-conforming material,

9.9.4.2 Divert to quarantine for subsequent analysis any identified potential non-conforming material, and

9.9.4.3 Shutdown the process.

### CLEANING PROCESS AND CLEANING VERIFICATION

9.10 The cleaning process and frequency of cleaning should be defined and the effectiveness verified periodically.

9.11 The design and verification of the cleaning process should consider:

9.11.1 Material holdup,

9.11.2 Degradation of the material within the process,

9.11.3 Microbiological growth,

9.11.4 Formation of chemical films,

9.11.5 The advantages and practicality of clean in place versus off-line cleaning,

9.11.6 Ability to remove cleaning agents, and

9.11.7 Required level of cleanliness.

9.12 The cleaning frequency may be defined in terms of:

9.12.1 Elapsed operating time,

9.12.2 Quantity of material processed, and

9.12.3 History of process conditions or deviations.

## 10. Specifications of Continuous Manufacturing Systems

### USER REQUIREMENTS

10.1 The requirement specification of a continuous process system, for example, for the purpose of invitation of tender or purchase should follow good pharmaceutical engineering practices.

10.2 For a continuous process particular consideration should be given to ensuring that the user requirement covers:

10.2.1 The required operating pattern of the plant, for example:

10.2.1.1 Operating hours,

10.2.1.2 Change over requirements, and

10.2.1.3 Degree of automation/manual intervention.

10.2.2 The range of required instantaneous production rate.

10.2.3 The required product output over a given period.

10.2.4 The expected nature of the input, intermediate, and output materials, for example:

10.2.4.1 Expected/allowable range of CQAs,

10.2.4.2 Flow properties (including electrostatic properties, etc.),

10.2.4.3 Exposure or other hazards, or any combination thereof (for example, explosion risks), and

10.2.4.4 Sensitivities to degradation.

10.2.5 The transformation steps required and associated kinetics, for example:

10.2.5.1 Expected/allowable range of CPPs,

10.2.5.2 Requirements for heat and mass transfer where appropriate for critical process steps,

10.2.5.3 Residence times required for specific transformations, and

10.2.5.4 Factors affecting rate and direction of wanted and unwanted transformations.

10.2.6 Expected requirements for material traceability, for example:

10.2.6.1 Relationships between product quality attributes and process parameters, and

10.2.6.2 Residence time and residence time distribution.

10.2.7 Expected methods for product quality measurement and verification, for example:

10.2.7.1 Established methods for measurement of critical properties.

10.2.8 Expected methods for product and process control strategies.

10.2.9 The identification and range of external factors or disturbances that can be reasonably expected to influence the process, for example environmental conditions (temperature or humidity, or both), etc.

10.2.10 Expected yield.

## SYSTEM SPECIFICATION

10.3 In the specification for a continuous process system for pharmaceutical manufacture, consideration should be given to the inclusion of the following:

10.3.1 Process principles and design methodologies used.

10.3.2 Expected range of attributes for the input and intermediate materials.

10.3.3 Target range of attributes for output materials.

10.3.4 The designed minimum and maximum throughput rates based on specified material attributes and operating conditions.

10.3.5 The target maximum and minimum production volumes over a defined period.

10.3.6 Proposed methods of measuring product quality attributes.

10.3.7 Proposed method for product and process control.

10.3.8 Proposed method by which off-spec material is defined, identified, and separated from on-spec material.

10.3.9 The anticipated operational regime and expected maximum run time.

10.3.10 Limits/normal operating ranges for process parameters which may affect product quality, for example:

10.3.10.1 Maximum and minimum temperatures, and

10.3.10.2 Rates for heating or cooling steps.

10.3.11 Expected key material properties at specific conditions which may affect the system design, for example, pH, Viscosity.

10.3.12 The proposed dynamic performance during transitions between the various operating states (for example, startup/shutdown time).

10.3.13 The identification and range of external factors or disturbances that can be reasonably expected:

10.3.13.1 The intended quantity of "material in process," that is, how much material is held in the plant during normal operation (entrained material)?

10.3.13.2 The intended "minimum operational volume," that is, how much material is required to be processed before steady state conditions are most likely reached?

10.3.13.3 The intended "time/material required to steady state," that is, How much material is required to be processed before on-specification (on-spec) product can be collected at the outlet of the plant?

10.3.13.4 "The intended material kept in process," that is, how much material is left in the plant when it is shut down?

10.3.14 Limitations on available resources and infrastructure, for example, footprint, headroom, structural load capacity, utilities.

## 11. Keywords

11.1 application; continuous processing; pharmaceutical industry

# APPENDIXES

**(Nonmandatory Information)**

## X1. EXAMPLES OF PROCESS DYNAMICS

### X1.1 Plug Flow System (See Fig. X1.1)

X1.1.1 Output response of system is equal to the input (subject to any time delay), that is:

X1.1.1.1 Rapid transition of CPP to change in set point, and

X1.1.1.2 Rapid transition between materials with differing CQA values.

X1.1.2 This type of response may be desirable in terms of precise tracking and identification of materials but requires very precise control of the system.

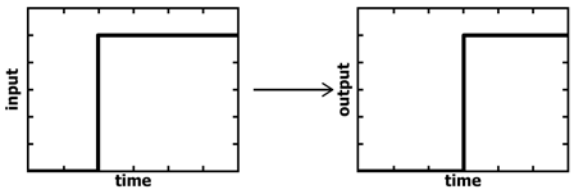


FIG. X1.1 Plug Flow System

### X1.2 Impact of Back Mixing (See Fig. X1.2)

X1.2.1 In addition to any time delay, the response of the output to the input change now occurs progressively.

X1.2.2 When applied to material CQAs, this type of response indicates the presence of back mixing within the system.

X1.2.3 A similar response in CPP values, for example, temperatures would represent the effect of thermal capacity/inertia in the system.

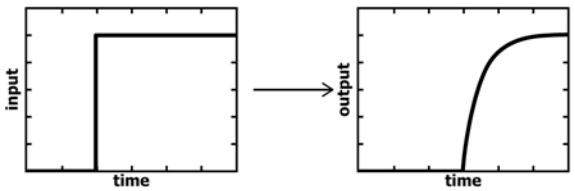


FIG. X1.2 Impact of Back Mixing

X1.2.4 This type of response may make the system slower to respond and less sensitive to minor variations hence more naturally stable.

X1.2.5 However long time constants and high levels of back mixing may make precise material identification and process control difficult.

## X2. COMPARISON OF CONTINUOUS AND BATCH PROCESSING

X2.1 See Table X2.1.

**TABLE X2.1 Comparison of Continuous and Batch Processing**

| Ref | | Continuous Process | Discrete Process | Implication |
|---|---|---|---|---|
| 1 | Addition of raw materials | Constantly added to the process, normally at a controlled rate. | Added only at the start of the process or at discrete events during the process. | CP requires capability to control flow rate of raw materials in real time. This is different to dispensing of total weight for a batch process. |
| 2 | Transformation of materials | Material exists simultaneously in all conditions between the starting conditions of the raw materials through to the finished condition of the final product.<br>The gradient between raw material and finished product exists in space. | All material within the process is nominally in the same state of transformation at the same time.<br>The gradient between raw material and finished product exists in time predominantly. | Systems designed to measure and sample product attributes in a CP system must be able to collect and analyse data as the product flows past the measurement/ sample point at a frequency which ensures that no product which might be out of specification will be released. |
| 3 | Time profile of intended process | The process parameters will be controlled in order to achieve a target "steady-state" condition for the material properties.<br>The target steady-state condition of the material properties at a point in the process may be time invariant (for example, extrusion, milling, or roller compaction) or in a quasi-steady-state system may consist of a large number of repeated cycles of similar process conditions within one production run (for example, tablet press). | Process conditions follow a single change trajectory from start to end of the production run. | In a batch process it is possible to adjust the process duration for the complete batch in order to ensure the correct process end point (for example, granulation end point).<br>This is not possible in a continuous process and hence the system must be designed in a way that the equipment design (for example, design parameters which influence the residence time and residence distribution) is well defined and understood and to ensure that other parameters (for example, product flow rate or energy input) can be adjusted in order to deliver the correct product transformation. |
| 4 | Discharge of finished product | Product is removed from the process while the transformation process continues for material remaining in the process. | Material is removed once all material has been transformed into finished product. | This provides the opportunity to adjust process parameters for material which has yet to be produced based on material already produced.<br>It also means that it cannot be assumed that all material is homogeneous based on "stratified" sampling of the final product in bulk after it has been discharged from the process. |
| 5 | Process information | Information about the product properties or process condition may be regularly collected as material passes through each measurement point in the process.<br>This has the potential to generate a higher number of data points per Kg of product manufactured. | Information about each transformation of the whole batch of material is collected sequentially.<br>This generally results in fewer data points per Kg of product manufactured | It is important to understand the relationship between:<br>· The flow pattern and rate of material adjacent to the sensor.<br>· The volume of material measured by the sensor<br>· The rate at which the sensor can collect data relative to the local flow pattern<br>· The scale of scrutiny required |
| 6 | Detection and correction of variations from optimal target product quality | Potential to detect variations in raw material properties or product quality and apply corrective action to the process conditions while it is running such that subsequent product is closer to the optimal target quality (that is, to take benefit of the continuous process monitoring and trending, taking the opportunity to detect variations from target quality early on and to adjust the CPPs, in order to ensure uniform target quality being met). | Any variation detected affects the whole batch.<br>Any corrective action affects the whole batch and some forms of corrective action can only be applied if the process is reversible. | It is important to be able to differentiate between:<br>(*a*) The normal variability of a capable process which will continue to produce good quality product and where no action is needed, and<br>(*b*) Variability which will result in poor quality product if no corrective action is taken in a timely manner.<br>Appropriate tools are needed to ensure appropriate corrective action without introducing instability as a result of "over control." |
| 7 | Elimination of nonconforming product | Potential to design systems that are able to reject small quantities of nonconforming product (although this capability should not be seen as an alternative to developing a stable and well-controlled process). | Whole batch is homogeneous, and hence, if product does not conform, the whole batch will be rejected. | If off-spec material is produced during the operation of a continuous process, then the system must provide detection and rejection capability to eliminate this material from the process such that there is no risk that it can adulterate material which will be released to market. |

**TABLE X2.1** *Continued*

| Ref | | Continuous Process | Discrete Process | Implication |
|---|---|---|---|---|
| 8 | Amount of material affected by product quality decisions | The amount of material affected by a product quality decision may be flexible and potentially independent of equipment scale.<br>It may be determined based on risks associated with possible variance in incoming raw material and process parameters or on business needs. | Amount of material subject to a product quality decision is determined by the scale of production equipment and the validated process. | In a continuous process it is important to understand how much material is reliably represented by each measurement.<br>Processes with longer time constants will intrinsically be more stable but in processes with more back-mixing (which results in a longer time constant, that is, in process where a certain residence time distribution is required to meet process requirements, alike in blending processes) more material may be affected in the event of production of off-spec.<br>Thus, in general, easiest to control and trace are processes with a narrow RTD and a long time constant. |
| 9 | Product quality Acceptance criteria | Determined by the acceptable variability of operating conditions and either:<br>(*1*) Consistent acceptable quality and homogeneity of product measured at appropriate intervals during production.<br>(*1*) Consistent acceptable quality and homogeneity of all material collected together and measured in an appropriate way based on the risk of product variability as determined by the conditions during the process. | Determined by the acceptable variability of operating conditions and:<br>Consistent acceptable quality and homogeneity of all material collected together as a single entity. | In a continuous process, it is important to develop acceptance criteria which recognize the difficulties in analyzing the large volumes of time based data which may be available and which use information from the process in order to ensure appropriate measurement of the product. |
| 10 | Process development | Ability to investigate a wide range of process conditions during a single process run.<br>Potential for greater productivity and reduced material consumption during development subject to considerations of internal mixing within the process. | Each process condition investigated as an individual batch at the appropriate scale. | Processes with short time constants and limited and well defined back mixing will enable process conditions to be varied more frequently whilst allowing collection of product which is fully representative of a specific set of process conditions. |
| 11 | Scale up | Opportunity for scale up can be based on duration of process operation.<br>Systems can be designed to allow development work to be carried out via short-run periods on production scale equipment.<br>Potential for scale up by means of increased running time at the same scale of equipment. Thus, scale up is possible also in CP setup, but equipment related scale factor lower than in batch today as time serves as additional “scale up factor” in CP. | Requires scale up of equipment size. | Continuous processing gives the potential to use less product during development activities. |

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