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Standard Guide for Application of Continuous Manufacturing (BioCM) in the Biopharmaceutical Industry[1]

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1. Scope

1.1 This guide is intended as a complement to Guide E2968. It provides key concepts and principles to assist in the appropriate selection, development, and operation of continuous processing technologies for the manufacture of biologically derived products.

1.2 Several of the principles covered in Guide E2968 are applicable to biomanufacturing. However, processes for biologically derived products differ from those for synthetic drugs in a number of fundamental ways in addition to their source (for example, format: aqueous liquids versus powders; scope: genesis to final formulation). This guide is intended to provide greater clarity for biomanufacturing. It does not imply that topics in Guide E2968 that are not covered here do not apply to continuous manufacturing (CM) for biologics.

1.3 Biologically derived products also differ widely from each other in terms of modalities, source materials, and the manufacturing technologies used, not all of which are equally amenable to operating in a continuous mode.

1.4 Opportunities do exist for the introduction of continuous technologies, for example, efforts are ongoing to adapt processes for large-scale manufacture of broadly applicable modalities such as monoclonal antibodies to a continuous format. This guide is intended to provide guidance to the design and implementation of antibody processes.

1.5 The principles can be applicable to unit operations or processes or both for other modalities but may not be applicable to all bioprocesses.

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

1.7 Since much of the processing is done under conditions amenable to microbial growth, maintaining process streams free from external biological impurities and microbial contamination (for example, bioburden, viruses, and mycoplasma) is critical.

1.8 This guide is intended to apply in both the development of a new process or the redesign of an existing one.

1.9 A manufacturer may choose to implement continuous manufacturing for discrete unit operations in stages as they develop process understanding before implementing a fully connected or continuous manufacturing process.

1.10 *Units*—The values stated in SI units are to be regarded as the standard. No other units of measurement are included in this standard.

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

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

2. Referenced Documents

2.1 *ASTM Standards:*[2]

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

E2475 Guide for Process Understanding Related to Pharmaceutical Manufacture and Control

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

E2888 Practice for Process for Inactivation of Rodent Retrovirus by pH

[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 E55.12 on Process Applications.

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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.

E2898 Guide for Risk-Based Validation of Analytical Methods for PAT Applications
E2968 Guide for Application of Continuous Manufacturing (CM) in the Pharmaceutical Industry
E3042 Practice for Process Step to Inactivate Rodent Retrovirus with Triton X-100 Treatment
E3051 Guide for Specification, Design, Verification, and Application of Single-Use Systems in Pharmaceutical and Biopharmaceutical Manufacturing
E3077 Guide for Raw Material eData Transfer from Material Suppliers to Pharmaceutical & Biopharmaceutical Manufacturers
E3231 Guide for Cell Culture Growth Assessment of Single-Use Material
E3244 Practice for Integrity Assurance and Testing of Single-Use Systems

2.2 *ISO Standard:*
ISO 20399 Biotechnology—Ancillary materials present during the production of cellular therapeutic products and gene therapy products[3]

2.3 *Regulatory Documents:*
EMA/CHMP/BWP/187338/2014 Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission April 28 2016[4]
FDA Guidance for Industry PAT A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance[5]
FDA Guidance for Industry Process Validation: General Practices and Principles, rev1[5]
FDA Quality Considerations for Continuous Manufacturing Guidance for Industry[5]

3. Terminology

3.1 *Definitions*—For general definitions, refer to Terminology E2363 and Guides E2537 and E2475. For definitions specific to continuous manufacturing, refer to Guide E2968 and ICH Q13 (**1**).[6] In 3.2, clarification of how they are applied to bioprocesses is provided.

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *back-mixed process, n*—process with a residence time distribution (RTD) whose breadth is potentially significant compared to the mean residence time.

3.2.1.1 *Discussion*—Certain steps in biomanufacturing are fully back mixed (for example, in the case of a bioreactor or for a pooled load to a subsequent step) and 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 as a more gradual change. The rate of this change will depend on the equipment characteristics, residence volume, and the residence time distribution/degree of mixing. A fully back-mixed process may be considered and modeled as one or more continuously stirred tank reactors (CSTR). The process to produce a biologic product may contain different modes of manufacturing steps such as batch processing and semi-continuous and continuous processing steps. For example, the process to make product can be based on a batch process in a seed expansion stage followed by a continuous process in which the cells are growing continually in the bioreactor while media and nutrients are pumped into the vessel and cells and product are removed from the bioreactor as an upstream process. The downstream separation of the cells from the media, and each of the subsequent purification steps, may be run in batch mode or in a semi-continuous or continuous mode based on different manufacturing technologies. If the subsequent steps of the continuous process step are run in a batch mode as multiple lots, then the product from the continuous process is collected over time. This material may be concentrated or is fed to the subsequent batch step within predefined ranges for collection, mixing, and hold conditions that assure the solution's stability over the time the material is collected.

3.2.2 *batch (or lot), n*—specific quantity of material produced in a process or series of processes that is expected to be homogeneous within specified limits.

3.2.2.1 *Discussion*—In continuous manufacturing (CM), a batch may correspond to a defined fraction of the production for either a fixed quantity of material or by the amount produced in a fixed time interval at constant flow rate. Note that multiple lots of raw materials may be used during a CM process, and it is important to ensure traceability to source in the event of an excursion at any point.

3.2.3 *dynamic process control system, n*—process dynamics refer to the response of a manufacturing process to changing conditions or transient events.

3.2.3.1 *Discussion*—An automated control system is one that *(1)* monitors the condition of the product or the process or both, *(2)* predicts or detects a change to the process indicators or product quality away from a target condition, and *(3)* then changes the process conditions during manufacturing to maintain the product quality at the target value (or within the specified range of target values). An example in a continuous process producing a biologic would be controlling the cell density within a specific range in a perfusion bioreactor by continuous cell removal ("cell bleed"). Maintaining the density within that range provides for a higher assurance that the growth rate is constant, the productivity is similar, and the material produced has the desired characteristics. Depending on the dynamics of the process step, 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 feedback, feed forward control, or 3.2.3.2.

3.2.3.2 *multivariate model-based control, n*—measurements of one or more product attributes and process conditions are used in a mathematical model of the process or process step to

[3] Available from American National Standards Institute (ANSI), 25 W. 43rd St., 4th Floor, New York, NY 10036, http://www.ansi.org.
[4] Available from the European Medicines Agency (EMA), Domenico Scarlattilaan6, 1083 Amsterdam, The Netherlands, www.ema.europa.eu.
[5] Available from U.S. Food and Drug Administration (FDA), 10903 New Hampshire Ave., Silver Spring, MD 20993, http://www.fda.gov.
[6] The boldface numbers in parentheses refer to the list of references at the end of this standard.

determine the process conditions required to achieve the desired outcome depending on the operational objective (for example, cell viability, product titer, and purity) and process parameters are adjusted as needed based on the output from the model (that is, dynamic control element). It aligns with multivariate statistical process control, the application of multivariate statistical techniques to analyze complex process data with potentially correlated variables. Note that univariate controls are also valid.

3.2.4 *continuous manufacturing (CM) or manufacturing step/unit operation, n*—involves the continuous feeding of input materials into, the transformation of in-process materials within, and the concomitant removal of output materials from a manufacturing process or unit operation.

3.2.4.1 *Discussion*—

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

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

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

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

(2) A CM process or process step may be operated to transform a predefined quantity of material into a product with predefined quality attributes that is then subjected to either a disposition decision or a decision of the suitability based on the characteristics of the in-process material. The size of the resulting batch can be defined in terms of one of the following:

(a) Quantity of output material,

(b) Quantity of input material, and

(c) Run time at a defined mass flow rate.

(3) Other approaches to define batch size can also be considered, if scientifically justified based on the characteristics of the CM process. A batch size can also be defined as a range, for example, by defining the minimum and maximum run time.

(4) A CM process may be operated for an extended time. The quality and quantities of intermediate or finished 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. Note that in the case of bioprocesses, performance should be monitored to ensure that there are no changes over time. For example, cell-line expression level or product characteristics may change as the cell line ages or if the cell line is contaminated with another organism, such as mycoplasma or a virus. In the case of a purification step, the process parameters for example resin or membranes used should be monitored to detect changes that may impact product quality attributes or yield of the continuous process. For example, the lifetime of a resin or membrane should be determined using data or laboratory studies or both and an appropriate cleaning or replacement schedule or both developed to address buildup of material (fouling) and degradation. Minor changes in process attributes during the lifespan of a CM operation are acceptable as long as they remain within preestablished acceptance criteria.

(5) 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 that might be considered to be composed of a sequence of discrete events. An example of this is a continuous column purification process in which multiple columns run simultaneously, but each may be at a different stage (for example, loading product, washing, elution, regeneration and cleaning), independently of the other columns, such that a continuous or semi-continuous flow into the column purification step and out of the column purification step may be enabled.

(6) 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, startup and shutdown of production cell culture). This condition should not automatically invalidate the definition of the process as representative of normal continuous operation.

3.2.5 *process control setpoint, n*—specific target value for a process parameter or product attribute that is used by a dynamic control system.

3.2.5.1 *Discussion*—The dynamic process control system will determine what corrective control action to apply to bring the specific parameter or attribute closer to the setpoint value. 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 specified 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.

3.2.6 *process disturbance, n*—unplanned change to process inputs beyond the normal operating range or conditions (for example, process parameter, material property, equipment condition, or environment) that are introduced into a system.

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

3.2.8 *recipe-based process control system, n*—automated control system that maintains specific process parameters at prespecified 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.

3.2.9 *residence time, n*—time that process material is in a specific process environment/vessel/unit operation.

3.2.10 *steady state, n*—stable condition that does not change over time.

3.2.10.1 *Discussion*—

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

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

(3) Process parameters can vary within a specified range in a steady state process. While critical parameters shall remain within a specified tolerance, other parameters may exhibit typical process variability.

3.2.11 *transient event, n*—temporary condition in which a process goes through a dynamic change.

3.2.11.1 *Discussion*—This change may be due to a disturbance or an intentional alteration in the selected operating conditions (for example, startup, shutdown, or changes from one operating condition to another). Development of a continuous process should include mitigations to prevent process-related transient conditions from unacceptably affecting product quality. Examples that can result in transient conditions are changes in raw material batches, fouling, a temperature shift in a cell culture process, or a change in the product quality attributes from one process step to another over time. Mitigations could include diversion to quarantine while the impact of the conditions on product quality is assessed.

4. Significance and Use

4.1 This guide focuses on upstream and downstream processes for biopharmaceutical products with a particular focus on antibody production processes. For further information, see Appendix X1 and Refs (**1-3**).

4.2 Bioprocesses traditionally consist of discrete unit operations labeled as upstream, downstream, and fill/finish operations. The objectives at each stage are significantly different, as are the operating parameters and control processes, that can make complete integration impractical initially (Appendix X1). This guide does not imply that complete integration is a prerequisite. A higher degree of integration may be possible over time as a better understanding of the dynamics of processes become established.

4.2.1 *Upstream Processes*—The purpose of upstream processes is to generate sufficient product to meet patient requirements preferably in the fewest number of batches. This starts with increasing biomass (cell-line expansion from working cell bank to production inoculation) to a production bioreactor in which the focus shifts to producing product. The material within a bioreactor during extended growth is heterogenous, for example, cells will differ in age, there may be genetic drift, secreted product can differ in the residence time spent in the bioreactor, and cell debris accumulates throughout the process.

4.2.2 *Downstream Processes*—The purpose of downstream processes is to harvest product and purify it from process- and product-related impurities (for example, cell debris, nucleic acids, and misfolds) to the desired level. Solids are first separated from solutes; solutes are then separated from each other in the process of purification. Certain processes may at best be semi-continuous, and some steps may be prone to fouling, which may require manual intervention.

4.2.3 *Fill/Finish Operations*—The purpose of fill/finish operations is to formulate the purified product in a form that ensures stability and sterility and provides a dosage form consistent with the desired product profile. Operations may also include inclusion in a delivery system as a combination product. In this guide, operations up to and including final bulk fill for final drugs substance are addressed. Fill/finish operations for drug product and combination products are out of scope for this guide.

4.3 This guide does not advocate the following:

4.3.1 CM is suitable for the manufacture of all biopharmaceutical products and processes;

4.3.2 Guidance on issues related to the safe operation of a CM process or continuous biomanufacturing equipment. It is the responsibility of the user of this guide to establish appropriate health and safety practices and determine the applicability of regulatory limitations before use; and

4.3.3 Specific designs or operating regimes for CM.

5. Operation of Continuous Manufacturing Systems

5.1 *Operational Considerations:*

5.1.1 To introduce CM successfully, 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*—Use qualified scale-down models of the continuous process or process step to understand the variables that need to be controlled to produce a consistent product and small quantities of material under different operating conditions during the development of the product. Understanding the effect of process variables on product properties provides a basis for designing large-scale manufacturing processes.

(1) Within the qualified models, consider the uncontrolled variables that may change over time, for example, changes in the genetic makeup of the cells or changes in the proteins expressed by the cells over time and how that may impact product quality. A secondary consideration is the ability to detect and characterize process perturbations such as a contamination event.

(2) Consider the suitability of the model for manufacture of variable quantities of product at stable operating conditions for supplying the product to clinical trials supplies, if applicable.

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

(1) Increasing production by increasing run length duration/number of cycles provided there has been a prior verification on the permissible maximum duration of a unit operation [for example, cell culture, see 5.1.1.1*(1)*];

(2) Increasing production by addition of parallel processing lines;

(3) Increase in production rate;

(4) A risk-based approach to increasing the scale of CM process equipment;

(5) Which parameters can be appropriately characterized using a scale-down model (in smaller equipment) and which parameters are not effectively replicated by the model; and

(6) Responding to decreased demand in the same equipment by decreasing batch size/run duration/number of cycles.

Note that the change in duration/number of cycles can have an impact on validation for the reasons stated previously.

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

(1) The ability of the system to produce consistent product over the intended duration of the operation;

(2) Key parameters, sampling points, and process limits that assure that the process is in a state of control;

(3) Mechanisms of failure and degradation of performance together with appropriate methods of detection as this detection will likely be dependent on the process step being monitored;

(4) Qualification of recovery procedures in the event of excursions (minor nonconformance to catastrophic failure);

(5) Degree of redundancy in equipment and sensors required to assure continuous stable operation;

(6) Necessity and frequency for operator intervention to maintain normal operation (for example, filter fouling); and

(7) Run-to-run variability in process parameters.

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 (QA) personnel in the theoretical and practical aspects of continuous manufacturing;

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

(3) Use of equipment that is specifically designed for continuous manufacturing, was adapted for continuous manufacturing, or other technologies such as single-use (SU) equipment integrated into the manufacturing process. Most (but not all) SU equipment can be supplied presterilized and avoid the need for cleaning, in addition to operating as a closed system, which provides a high degree of assurance of sterility. See also Guide E3051.

(4) Appropriate procedure systems to account for real-time or near-real-time rapid release of process intermediates (note that hold times may be included/optional as breakpoints to manage the risk of product loss from an excursion further downstream).

5.2 *Operating States:*

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

5.2.1.1 A process may begin as a series of connected steps that are integrated progressively subject to appropriate regulatory approval before becoming fully continuous.

5.2.2 Risk analysis techniques, practical tests, modeling tools, or any appropriate combination of these should be used to ensure that all potential impacts on product quality are understood and appropriately managed over all potential operating states. For example, the following can be considered:

5.2.2.1 Equipment startup (for example, initialization and warmup ready for manufacturing);

5.2.2.2 Manufacturing startup (introduction of feed materials to start manufacturing and reaching a steady state);

5.2.2.3 Normal steady state as defined for a particular process step and in-specification operation (that is, verified to deliver material that is suitable to be released or move to a subsequent process step). As mentioned during this steady state operation, specific process characteristics of the cell line or the state of the equipment can be checked such that these variables remain within acceptable ranges or limits;

5.2.2.4 Transient operation during flow rate, unit operation changes, or maintenance (for example, replacement of filters as they foul or removal of product/cells at various points to maintain cell density levels);

5.2.2.5 Replenishment of feedstock materials, particularly considering the impact of any variability in raw materials and processing aids such as media, media feeds, buffers, and filter characteristics;

5.2.2.6 Process pause or hold or diversion to a surge vessel (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 or rejection of any residual material that does not or would not meet specifications;

5.2.2.9 Cleaning/sanitization/product/grade changeover;

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

5.2.2.11 Mechanically shut down and out of service.

5.2.3 In some defined circumstances, manufacturers of drug substance may reprocess or continue to process material held under quarantine provided the requirements for rework/reclaim of the production material are defined in a written procedure and rework/reclaim is approved by the quality authority to avoid supply disruption. European guidelines (EMA/CHMP/BWP/187338/2014) state that reprocessing can be considered in exceptional circumstances and when there is a clear identification of the root cause. Requirements are no less stringent than for traditional batch processes. Examples could include reprocessing of material in the event of a leak or filter failure or from a chromatography column in which performance deviates from criteria (for example, within specification, but exceeding action limits). PDA Technical Report 74 provides a detailed discussion of examples and both proactive and reactive approaches to reprocessing (**2**). Catastrophic failures (for example, gross leaks) are not included.

5.3 *Process Management:*

5.3.1 Processes can be sensitive to variability in materials, changes to the process, and/or equipment over time. A fully continuous biomanufacturing process (BioCM) or individual continual process steps may pose particular challenges because of behaviors of both equipment and materials that may be gradual or stochastic (for example, changes in gene expression or cell diameter) and the extended length of the run time. These changes may not be easily observed during batch processing, scaled-down models, or short test runs of continuous processes.

5.3.2 Suitable risk analysis, practical tests in-process testing strategies, and modeling techniques should be considered to determine and evaluate potential challenges in maintaining stable process conditions during the operation of a continuous process or a continuous process step over the full length of the required production run, and any sampling or data review as

part of this risk analysis and ongoing risk management can be done in consideration of ongoing process dynamics.

5.3.3 Consideration should be given to:

5.3.3.1 Management of bioburden and the avoidance of contamination events, which in worst-case scenarios can result in catastrophic failure and total plant contamination. These are not unique to continuous manufacturing but the combination of extended run times, longer processing times between equipment/flow path cleaning and sanitization, and increased process complexity can increase the risk of an adverse event.

5.3.3.2 Periodic cleaning and sanitization cycles should be qualified, designed into processes, and validated for effectiveness when the same equipment is used multiple times, for example, in a hybrid process in which multi-use equipment is used together with single-use components. Cleaning cycles are included in chromatographic processes to prevent fouling. Sanitization steps may be necessary depending on the way columns were prepared for use.

5.3.3.3 The potential for fouling and the creation of process impurities, for example:

(1) Fouling of equipment surfaces (for example, impact on heat transfer by product binding);

(2) Potential impact of binding to surfaces (for example, resins, filters) causing product and process modification over time;

(3) Ducts, pipes, and tubing changes over time (for example, impact on flow patterns);

(4) Fouling of instruments and probes (for example, impact on their accuracy and so forth);

(5) Fouling of filters and resins (for example, impact on flow and pressure of fluids);

(6) Byproducts with different or undesirable characteristics or both;

(7) Precipitation, aggregation, encrustation, and/or blocking of constrained flow paths;

(8) Leachables that could enter the manufacturing process during normal operation; and

(9) Creation of aggregates as a consequence of processing steps.

5.3.3.4 Note it should be accounted that the change out of a filter or resin can result in fluctuations in process streams (improved flow, increases in product concentration).

5.3.3.5 Changes in raw material behavior should be accounted between batches/sources/suppliers that may not be covered within existing quality control requirements, for example:

(1) Biochemical properties of materials and level of impurities,

(2) Electrostatic properties particularly in dried (lyophilized) biopharmaceuticals,

(3) Safety properties.

5.3.3.6 The impact may be on product quality or process performance or both.

5.3.3.7 There can be an impact of environmental changes on raw material and product, for example:

(1) Temperature,

(2) Relative humidity (RH),

(3) Age of raw material, and

(4) Light exposure (particularly plastic, single use equipment).

5.3.3.8 There can be changes in plant and equipment characteristics over time and with prolonged uninterrupted use, for example:

(1) Changes in surface finish and variability in cleaning of surfaces;

(2) Changes in clearances because of wear;

(3) Loss of sterility because of wear or improper cleaning methods; and

(4) Creation of leaks in vessels, tubing, and connectors not intended for multiple use.

5.3.4 The maximum length of run time of a process depends on the most critical component/step of the process that is susceptible to the extended length of operation and can impact the product significantly compared to other components or the steps within the process.

5.3.5 When a single-unit operation within a process line is determined to be disproportionally vulnerable to degradation in performance or sensitivity to variability, then strategies to maximize the potential run time to avoid the need to stop the overall process can be considered, for example:

5.3.5.1 Periodic/rapid replacement of individual items of equipment such as filters and membranes;

5.3.5.2 Redundancy (particularly for cell retention devices and membranes used in membrane-based steps), parallelization, or duplication of critical equipment elements (for example, cell concentration devices, filters, pumps, tubing, and critical in-process instruments used to measure process step control parameters); and

5.3.5.3 Process characterization to determine the degree and frequency of vulnerability of the unit operation and requirements for preventive maintenance.

5.4 *Requirement for Operator Intervention:*

5.4.1 Generally, a CM can be expected to operate with the minimum practical level of operator intervention.

5.4.2 Certain types of intervention can be planned and a course of action determined in the event of, for example, leaks, filters, or resins fouling.

5.4.3 Unplanned operator intervention should be considered as a potential source of uncontrolled variability. Continued unplanned intervention may indicate inadequacies in process design, lack of understanding of the critical process variables, or uncontrolled or unmanaged variability in process conditions or raw material properties.

5.4.4 Continuous improvement tools (for example, real-time statistical process control and process automation) can be used during operation to identify the causes of any unplanned operator intervention. 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 a CM Process

6.1 *Principles:*

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

6.1.2 However, the design of the CM process may require the consideration of additional factors that are not as important in a batch process, such as fouling potential of cell retention devices, product pooling, and fault recovery strategies (a manufacturer may choose to include specific pooling steps at strategic points in the process as a precautionary measure to avoid/minimize loss of material in the event of an issue).

6.1.3 Hence, when designing a continuous biomanufacturing 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 and buffer capacities of each unit operation to ensure that the desired process conditions and overall line flow rates under the required operating regimes can be achieved. Some examples are:

(1) Balancing the inflow rate of media into the bioreactor, with the outflow of product, and drawing off of cells to maintain a consistent cell density in the bioreactor growing at an appropriate doubling time;

(2) The capacity of a cell removal system can be examined to ensure that it corresponds to the volume and flow rate of the cell suspension entering into the cell removal step; and

(3) The rate, flow, and concentration of an unpurified protein solution entering into a continuous purification step can be managed throughout the individual cycles within the step. The flow rate of non-loading steps (for example, cleaning, regeneration) may be modified to balance with the duration of loading steps. This will be dependent on load concentration, load flow rate, resin dynamic binding capacity, column volume, and the number of columns;

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 to achieve a specific productivity within the bioreactor or specific purity within a continuous purification system;

6.1.3.6 The process time constants, reaction rates, average, maximum, and minimum residence times required to achieve a specific process objective such as specific product quality (glycosylation, recovery, purity);

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 or continuous process step using process and chemical engineering principles, for example:

(1) Capacity of physical transfer systems,

(2) Capacity of heating systems, and

(3) Sufficient supply of nutrients and removal of by-products for a growing cell culture; and

6.1.3.9 Implementation of appropriate monitoring tools.

6.2 *Process Time Constants:*

6.2.1 The time available for a given bioproduct production or purification is determined by the residence time of the material in a specific process step based on the environment in the bioreactor or purification step. The focus is the time required to produce material in the desired final conditions.

6.2.2 As the material flows through a particular CM system or step, rate-limiting elements within the process shall 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, the following should be considered:

6.2.2.1 Product binding and elution in a continuous purification step,

6.2.2.2 Ensuring a minimum hold time at a specified condition for a viral inactivation step, and

6.2.2.3 The time for startup and transient conditions for a continuous cell culture process.

6.2.3 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 startup and shutdown and, hence, the impact on quality decisions regarding the disposition of material manufactured during this period.

6.2.4 Consideration should be given to the use of monitoring systems that determine if the required product attributes or process indicators are achieved before product 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 To characterize a continuous process, the process residence time and residence time distribution within the CM step shall be understood and quantified during both startup and normal operation as well as during process disturbance and shutdown conditions. This is particularly important when the step is dynamically changing, for example, drug substance production within a continuous cell culture bioreactor.

6.3.2 The mixing of product within the system is important. For each continuous step, the following should be considered:

6.3.2.1 Process modeling of each continuous step and integration with prior and following steps (as appropriate),

6.3.2.2 Validation tests using specific markers/tracers, and

6.3.2.3 Online/inline process measurement of appropriate process indicators and product attributes.

6.3.3 Two extremes of mixing are commonly identified as “plug flow” or “fully back mixed.” Bioreactor processes have a high degree of mixing. Product that has been produced by cells in the bioreactor, but not yet removed, may be degraded by host cell impurities that are retained in the bioreactor.

6.3.4 An estimation of the residence time distribution (RTD) within the process enables an understanding of:

6.3.4.1 Which output material contains which input material,

6.3.4.2 Which 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 In particular, quantification of the residence time distribution may be used to ensure that product remains within the predefined process conditions. This understanding is particularly important in live cultures of cells in which strict