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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 Process Analytical Technology in the Pharmaceutical 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

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

[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 E55.04 on General Biopharmaceutical Standards.

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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.

E2968 Guide for Application of Continuous Processing 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 determine the process conditions required to achieve the desired outcome depending on the operational objective (for

[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.

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.