Quality Considerations for Continuous Manufacturing

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2019
Pharmaceutical Quality/CMC
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Quality Considerations for Continuous Manufacturing

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Quality Considerations for Continuous Manufacturing Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information regarding FDA's current thinking on the quality considerations for continuous manufacturing of small molecule, solid oral drug products that are regulated by the Center for Drug Evaluation and Research (CDER). The guidance describes several key quality considerations and provides recommendations for how applicants should address these considerations in new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplemental NDAs and ANDAs, for small molecule, solid oral drug products that are produced via a continuous manufacturing process. FDA supports the development and implementation of continuous manufacturing for drug substances and all finished dosage forms where appropriate, including those submitted in NDAs, ANDAs, drug master files (DMFs), biologics license applications (BLAs), and nonapplication over-the-counter (OTC) products. Scientific principles described in this guidance may also be applicable to continuous manufacturing technologies used for these drugs. However, this guidance is not intended to provide recommendations specific to continuous manufacturing technologies used for biological products under a BLA.

For purposes of this guidance, FDA considers "continuous manufacturing" to be a process in which the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system.[2] Although this description can be applied to individual unit operations or a manufacturing process consisting of a series of unit operations, as described in this guidance, continuous manufacturing is an integrated process that consists of a series of two or more unit operations.

This guidance focuses on scientific and regulatory considerations that are specific or unique to continuous manufacturing. These considerations include process dynamics, batch definition, control strategy, pharmaceutical quality system, scale-up, stability, and bridging of existing batch manufacturing to continuous manufacturing. Recommendations broadly applicable to both

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] "The system" is the integrated process that consists of a series of two or more unit operations.

continuous and batch processes are generally not covered in this guidance and the reader should refer to other FDA and International Council on Harmonization (ICH) guidance documents for such information.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA is committed to supporting and enabling pharmaceutical innovation and modernization as part of the Agency's mission to protect and promote public health. The Agency hopes that these efforts may also help reduce the number of drug shortages, as noted in FDA's drug shortage strategic plan.[3] In 2002, FDA launched an initiative entitled "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach," to encourage the implementation of a modern, science- and risk-based pharmaceutical quality assessment system.[4] One goal of the initiative is to ensure that regulatory review, compliance, and inspection policies continue to support continuous improvement and innovation in the pharmaceutical manufacturing industry. Since publication of that initiative document, FDA has promoted a vision of a maximally efficient, agile, flexible manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.

FDA supports the adoption of modern manufacturing technology as a foundation for improving the overall quality of products and availability to patients. FDA recognizes that continuous manufacturing is an emerging technology that can enable pharmaceutical modernization and deliver potential benefits to both industry and patients. Continuous manufacturing can improve pharmaceutical manufacturing by, for example, using an integrated process with fewer steps and shorter processing times; requiring a smaller equipment footprint; supporting an enhanced development approach (e.g., quality by design (QbD) and use of process analytical technology (PAT) and models); enabling real-time product quality monitoring; and providing flexible operation to allow scale-up, scale-down, and scale-out to accommodate changing supply demands. We also expect that this operational flexibility may decrease the need for some postapproval regulatory submissions. Therefore, FDA expects that adopting continuous manufacturing for pharmaceutical production will reduce drug product quality issues, lower manufacturing costs, and improve availability of quality medicines to patients.

[3] See FDA's Strategic Plan for Preventing and Mitigating Drug Shortages (October 2013) at: https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf.

[4] See Pharmaceutical cGMP's for the 21st Century: A Risk-Based Approach (September 2004) at: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/manufacturing/questionsandanswersoncurrentgoodmanufacturingpracticescgmpfordrugs/ucm176374.pdf.

III. QUALITY CONSIDERATIONS

A. Key Concepts of Continuous Manufacturing

1. Process Dynamics

Product and process understanding form the foundation for effective risk management.[5] The expectations regarding the science- and risk-based approach to the control of processes and product quality based on process understanding are the same for continuous manufacturing as for traditional batch manufacturing.[6]

Continuous manufacturing processes are dynamic systems, unlike batch manufacturing processes. During normal operation, a set of critical process parameters and/or quality attributes are kept close to the target values, rather than at a steady-state condition. Transient disturbances may occur during normal operation. These are usually small enough to be controllable (i.e., being kept within a desired range). Larger changes in process parameters and quality attributes can happen when a process is in a transient state, such as during start-up and shutdown, a change from one operating condition to another, or significant deviations such as those due to equipment failure or unexpected change in material attributes. Understanding of process dynamics as a function of input material attributes (e.g., potency, material flow properties), process conditions (e.g., mass flow rates) or equipment design elements (e.g., blade types for a continuous blender) enables material traceability (the ability to preserve and access the identity and attribute of a material throughout the system) during and after production. This knowledge is essential for identification and mitigation of risks to product quality. Therefore, due to the dynamic nature of continuous processing, the risk assessment for a continuous manufacturing process should consider process understanding of the integrated system in addition to each unit operation.

A suitable scientific approach should be used to characterize how a material flows through the process. One common approach is characterization of residence time distribution (RTD) for the individual unit operations and integrated system. An RTD is a probability distribution that describes the amount of time a mass or fluid element remains in a process, and can be measured through a tracer experiment, online process measurements of appropriate product attributes, and/or process modeling. The shape of the RTD reflects the degree of axial dispersion or back mixing within that system, which affect the propagation of disturbances, material traceability, and the control strategy (e.g., material diversion and sampling frequency). The RTD is dependent upon several factors such as input material attributes, mass flow rates, process parameters, and equipment design and operation. It is important to understand how the RTD varies over the range of planned operating conditions in addition to characterizing the RTD at the nominal/target operating conditions. This information serves as a basis for material traceability and

[5] See guidance for industry *Q9 Quality Risk Management* (June 2006) and *Q10 Pharmaceutical Quality System* (April 2009).

[6] See Pharmaceutical cGMP's for the 21st Century: A Risk-Based Approach (September 2004) at: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/manufacturing/questionsandanswersoncurrentgoodmanufacturingpracticescgmpfordrugs/ucm176374.pdf.

determination of appropriate sampling plans and is essential to designing a control strategy for continuous manufacturing processes.

2. Defining Batches for Continuous Manufacturing Processes

The definition of a batch has regulatory implications, particularly with respect to current good manufacturing practice (CGMP), product recalls, and regulatory decisions. The terms *batch* and *lot* are defined in the regulations (21 CFR 210.3) as follows:

- Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.
- Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits.

These definitions for both batch and lot are applicable to continuous manufacturing. A batch can be defined based on the production period, quantity of material processed, quantity of material produced or production variation (e.g., different lots of incoming raw material), and can be flexible in size to meet variable market demands by leveraging the advantage of operating continuously over different periods of time. A lot may also be considered a sub-batch. The actual batch or lot size should be established prior to the initiation of each production run.

For batches that are defined based on time (e.g., a production period), a connection between material traceability and batch must be established to identify the specific quantity of the drug (21 CFR 210.3).

B. Control Strategy

Establishing, maintaining, and refining a control strategy is a life cycle activity – from development to technology transfer to ongoing verification during the commercial manufacturing phase – and is supported by pharmaceutical development, quality risk management, and a robust pharmaceutical quality system (PQS). An effective PQS strengthens the links across the stages of a product's life cycle and enables the development and continuous improvement of the control strategy.[7] This section provides considerations for the control strategy in the framework of a robust PQS for a continuous manufacturing process.[8]

[7] See guidances for industry *ICH Q8 (R2) Pharmaceutical Development* (November 2009), *ICH Q9 Quality Risk Management* (June 2006), and *ICH Q10 Pharmaceutical Quality Systems* (April 2009). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[8] Refer to 21 CFR 211 subpart F, Production and Process Controls for related regulations.

In general, in developing a *control strategy*,[9] manufacturers should consider unexpected and expected variations. For continuous manufacturing processes, this is even more critical, as there may be transient disturbances in input material attributes, process conditions, or environmental factors over time during normal operation. An effective control strategy for this continuous mode of operation should place special emphasis on mitigating the risk of these potential disturbances to product quality. To maintain a process within a state of control during continuous operation, detect temporary process disturbances, and segregate the resulting nonconforming materials from the system, manufacturers should increase the use of in-process control strategy elements.

The following describes recommendations for key aspects of the control strategy for a continuous manufacturing process.

1. Input Material Control

In a continuous manufacturing process, input materials are continuously added through a feeder system (e.g., loss-in-weight feeders for solid powders or pumps for liquids) over the duration of a production run. Different batches of input materials can be introduced to the system at different process time points, and variability in input material attributes could affect feeding, introduce process variability into the system, impact RTD models, and potentially affect finished product quality. In addition, transport processes in the integrated system may cause some degree of transformation (e.g., segregation or aggregation of powders). Therefore, continuous manufacturing may warrant additional characterization and control of input material attributes beyond compendial standards. Suitable risk analyses, experimental investigation, and/or modeling and simulation should be considered throughout the life cycle of the product, including during pharmaceutical development, to evaluate potential impact of material attributes (e.g., particle size distribution and density of the active pharmaceutical ingredient (API) and excipients) on the material flow properties, process dynamics, and quality of a final product over the period of an intended production run.

A formal monitoring program can be useful for manufacturers to identify changes in high risk raw material properties (e.g., inter-batch, intra-batch, and shifts over time) and proactively identify and mitigate the impact of these changes on the manufacturing process and the finished drug product.

Manufacturers planning to switch from batch to continuous manufacturing should take a similar approach to re-evaluate the existing specification(s) for raw materials and their use in a particular continuous process design.

2. Process Monitoring and Control

Implementation of a well-justified process monitoring approach is an element of the control strategy for any drug manufacturing process. For continuous manufacturing processes, process

[9] See guidance for industry *ICH Q8 (R2) Pharmaceutical Development* (November 2009) for the definition of *control strategy*.

monitoring and utilization of PAT tools[10] generate real time information on process parameters and attributes of input materials, in-process materials, and final products for the duration of the manufacture. This information can enable high detectability of transient disturbances and process deviations, active process control, more accurate material diversion, and real time release testing (RTRT).[11] A process monitoring approach should include at least the following:

- Variables being monitored at appropriate locations in the process, such as:
    - Process parameters,
    - Input and in-process material attributes, and
    - Final product attributes.
- Sampling plan, including:
    - Sampling locations,
    - Sampling or measurement frequency,
    - The sample size to be taken and measured, and
    - Statistical criteria appropriate for use to evaluate the process monitoring data.
- Type of analyses for process monitoring data, such as:
    - Univariate analysis based on control limits,
    - Multivariate or process model, and
    - Inter- and intra-batch trend analysis (e.g., moving averages and variance analysis).
- Intended use(s) of process monitoring data, such as:
    - Supporting other control strategy elements (e.g., active process control, material diversion, RTRT, batch release),
    - Evaluating process and equipment performance as part of process development, during manufacturing, and to facilitate continued process verification,
    - Ongoing monitoring of a process to confirm that it remains under a state of control, and
    - Additional elements of the Pharmaceutical Quality System.[12]

Developing the measurement system and sampling plan for process monitoring warrants several considerations. To determine which variables need to be monitored, the relationships linking material attributes and process parameters to product critical quality attributes (CQA) should be

[10] For details regarding PAT tools, refer to guidance for industry *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (September 2004). The PAT tools described in this guidance encompass spectroscopic and chemometric tools as well as non-spectroscopic sources and soft sensors. ASTM E2629 Standard Guide for Verification of Process Analytical Technology (PAT) Enabled Control Systems may be another useful document.

[11] See guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).

[12] Refer to section III.D, Additional Pharmaceutical Quality System Considerations.

understood.[13] The sampling plan should consider the intended use of process monitoring data and the impact of process dynamics on measurement frequency. The measurement equipment (e.g., the location of a sensor) should be evaluated to achieve representative sampling and avoid interference with the process.

Development of the process monitoring approach should include a risk assessment that includes consideration of how lapses in process monitoring data collection (e.g., recalibrating a near infrared (NIR) probe or refilling a feeder) might affect product quality.[14] The process monitoring approach selected should include alternative or additional quality controls to mitigates the risks to product quality posed by these scenarios.

Active process control requires that some parameters in the system have the capability to be adjusted in real time to reduce the risk of producing nonconforming materials. In this context, predefined process adjustments would not necessarily represent a departure from a state of control. An approach that includes implementation of active process control can include operator actions, increased sampling frequency, and automated feedforward/feedback controls, among other strategies. The establishment of appropriate limits (e.g., alarm or action limits) is also important for robust process control. The limits of acceptability for controls that ensure monitored critical process parameters and critical material attributes stay within desired ranges should be specified in the regulatory submission.

3. Material Diversion

A continuous manufacturing process is expected to maintain a state of control[15] and produce a product with desired quality. However, the manufacturing process will include periods when nonconforming material is produced, such as during start-up, shutdown, or temporary process disturbances. If the approaches for material traceability (see section A.1), process monitoring (see section B.2), and material removal are well established, this nonconforming material can be segregated and removed without affecting the rest of the batch.

In a period when nonconforming material is produced, the amount of diverted material should depend on the duration and severity of the disturbance, system process dynamics, and location of a diversion point. Studies of process dynamics, including RTD and disturbance propagation through the process, form the basis for determining the appropriate amount of material for diversion. The design of the system should consider including diversion points at commencement or completion of significant phases of production.[16] Design of the diversion point(s) locations should also consider feasibility of removal of material, the effect of location on the amount of material affected (e.g., dispersion of nonconforming materials via back-mixing or material transformation in the subsequent steps), and the effect of nonconforming material on

[13] See guidance for industry *Q8(R2) Pharmaceutical Development* (November 2009).
[14] See guidance for industry *Q9 Quality Risk Management Development* (June 2006).
[15] For the definition of s*tate of control*, see guidance for industry *ICH Q10 Pharmaceutical Quality System* (April 2009).
[16] See 21 CFR 211.110(c).

downstream processing. The establishment of safety margins to prevent nonconforming material from collection with acceptable material is recommended.

The manufacturer should establish procedures describing when material identified as potentially nonconforming is to be diverted and collected. If material is diverted due to an unexplained discrepancy, the reason for the discrepancy must be appropriately investigated before dispositioning the batch.[17] Diversions that are the result of expected system operating conditions may not require an investigation under 21 CFR 211.192. When frequent or cyclical process disturbances occur within a single production run resulting in atypical low yield,[18] the entire batch may need to be rejected depending on the outcome of the investigation. As appropriate, investigations must extend to other potentially affected batches and products.[19]

4. Real Time Release Testing

Monitoring of a continuous manufacturing process using PAT tools can generate a large amount of real-time process and quality data during production, which can be used to support RTRT. Although RTRT is not a regulatory requirement for implementation of continuous manufacturing processes, it is encouraged and could be applied to some or all of the finished product quality attributes tested for release of the batch.

When the RTRT is adopted as a part of the control strategy, special considerations should be given to the sampling strategy. The implementation of RTRT includes in-process online, at-line, and/or inline sampling. The selected sample size or frequency should be representative of the batch and the approach should be justified using an appropriate statistical approach with respect to the quality assurance provided by the specific approach (e.g., confidence and coverage). For data collected at high frequency, statistical methods for large sample sizes should be applied to provide improved characterization of a batch. RTRT calculations should also consider the observed variance in CQAs over a multi-batch campaign to account for both intra- and inter-batch variability. Furthermore, procedures should be developed to establish a plan for RTRT to address potential gaps in PAT data (e.g., failure of the PAT equipment).

Models can also be used to support RTRT. The models used for RTRT are regarded as high impact models, as per the criteria outlined in the *Role of Models in Quality by Design (QbD)* section in the *ICH QIWG Points to Consider* document.[20] Examples of these models can include multivariate models to predict dissolution for release and calibration models associated with NIR procedures that are used for content uniformity and assay release testing. The *ICH QIWG Points to Consider* document provides guidance on the development, validation, life cycle maintenance, and documentation for the high impact models.

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[17] See 21 CFR 211.192.

[18] As with batch manufacturing, yield should be used as one criterion for determining whether the investigation of an entire batch is needed.

[19] See 21 CFR 211.192.

[20] See ICH QIWG Points to Consider (12/6/2011), http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_9_10_QAs/PtC/Quality_IWG_PtCR2_6dec2011.pdf.

The following are examples of quality attributes and considerations for RTRT implementation:

- Identity testing of finished products
    - The identity test should be capable of distinguishing between other products manufactured at the manufacturing facility.
    - The impact of any unique identifiers such as embossing and sample orientation on the test method should be examined.
    - If the identity test is performed on an intermediate instead of the finished product, controls should be in place to prevent potential human and/or system errors during the subsequent processing steps.
- Tablet assay and content uniformity by NIR[21]
    - The sample size and sampling frequency for the NIR measurement should be statistically justified to provide adequate quality assurance.
    - The measurement location should be representative of the finished tablet and minimize the potential for segregation to occur (e.g., feed frame of the tablet compression step or uncoated tablet). The NIR measurement of active concentration in the tablet should account for tablet weight in calculating the total active concentration in a tablet.
    - The PAT tool used for RTRT should be validated against the offline analytical method (e.g., High-Performance Liquid Chromatography).
    - The calibration model associated with the NIR method should be adequately developed and validated over the proposed operating ranges for commercial production.
- Model serving as a surrogate for the release test
    - The model should be developed by considering all variables that have the potential to impact the quality attribute and is typically a function of a relevant combination of measured material attributes and process parameters.
    - The model should be developed to account for the potential variations in material attributes and processing conditions expected during commercial production.
    - The model should be validated using a statistically sound approach and against corresponding release testing method(s), as well as demonstrate specificity (e.g., capability of detecting nonconforming product). The sample must pass a corresponding release testing method, if tested.[22]

[21] Refer to draft guidance for industry *Development and Submission of Near Infrared Analytical Procedures* (March 2015) at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM440247.pdf.

[22] See 21 CFR 211.165.

5. Specification

Finished product specifications are required for products manufactured in accordance with 21 CFR 314.50(d) and 21 CFR 211.165(a). The approach to establishing specifications for continuous manufacturing processes should follow ICH Q6A and B with special considerations given to the sampling approach. As described in the above section, the use of RTRT is encouraged as it generally incorporates an enhanced sampling plan more representative of the batch, enabling the manufacturer to use better predictive statistical tools. In the case where RTRT is adopted in lieu of offline, end product testing, the specification should also include a regulatory offline analytical method and associated acceptance criteria that will be used to assess product quality over the shelf life.

6. Equipment

Manufacturers using continuous manufacturing processes may need to run equipment for long periods of time to achieve the predetermined batch size. Equipment performance could decline gradually during the same run or after several repeated runs, due to fouling or normal wear and tear. Such a performance decline may not be observed in short development runs. Therefore, equipment for continuous manufacturing warrants the following additional considerations on qualification, maintenance, and cleaning.

Equipment qualification should address both individual unit operations and the integrated system. Qualification of the integrated continuous equipment should demonstrate that the equipment is adequate for its intended purpose.[23] Qualification protocols should be representative of expected operating conditions including flow rates, pressures, speeds, and the duration of a continuous run. The quality unit should establish acceptance criteria for equipment performance and stability (e.g., parameter variability and drifts, as well as the absence of detrimental events) to support the development and operation of continuous manufacturing processes. During equipment qualification, the functionality of equipment components should evaluate specific events, including those used for detection of disturbances and execution of material diversion (e.g., forced perturbations).

Throughout the product life cycle, the development and maintenance of the control strategy should take into account equipment failure modes to ensure that abnormal equipment performance is detected and investigated, including appropriate corrective action. Equipment maintenance and calibration procedures should be developed and updated based on ongoing monitoring of equipment performance and other available information (e.g., experience with the equipment, equipment design, knowledge gained during the development and qualification results). The process monitoring strategy should include indicators of equipment performance based on qualification experience and understanding of potential failure modes. This can also help to determine the maximum run time for the integrated line before maintenance or cleaning is needed.

[23] Refer to 21 CFR 211 subpart D, Equipment.

Cleaning approaches should be developed and defined based on understanding obtained from development and scale-up (e.g., increased production run time) studies, and then be periodically verified to confirm continued effectiveness. Cleaning procedures should be established based on close monitoring of materials during operation and after disassembly, and should include, for example, examination of material hold up and build up on equipment, piping, filters, and instruments (e.g., online analyzers and sensors), degradation of material within the processing line during operation, chemical film formation, and microbial growth. The conditions evaluated during cleaning validation should take into account the potential failure modes (e.g., fouling) under the anticipated worst-case scenario (e.g., an extended production run time) based on the risk to the product quality or the risk of contamination to other products manufactured at the facility.

Batch size and campaigning procedures should be established with consideration of the maintenance and cleaning requirements for the integrated line. In general, cleaning frequency for continuous manufacturing processes should be established based on elapsed operating time, quantity of material processed, history of process conditions or deviations, and product change-over, if applicable. Preventive maintenance timetables, equipment monitoring, and time and/or operational limits (e.g., amount of materials being processed) between cleanings should be periodically evaluated and updated as part of life cycle management.

7. System Integration, Data Processing, and Management

For real time process monitoring and decision-making to be feasible, the integrated equipment and control strategy requires a robust automated platform to orchestrate production. Because of the speed with which decisions must be made in continuous operation, quality unit oversight relies heavily on data and actions from the automated system. Therefore, the routine operational and material disposition decision-making should be integrated into the automated control system.

The design and validation of the automation system, as well as its integrated qualification along with the entire equipment train, are critical. Both process control functionality and quality unit oversight should be part of the system and software design.[24] Special considerations should be given when integrating equipment and software from multiple vendors (e.g., consistent coding of a single parameter tag between systems). During the integrated qualification of the automation system and manufacturing equipment, it is important to demonstrate the functionality of the whole system, which could include introducing disturbances or inducing failure modes to ensure that the system responds as designed.

Well-designed software and associated validation, equipment qualification, integration of quality decision making, and automation maintenance make it possible for a continuous process to

[24] There are industry standards that are helpful in validating the automation system. For example, see the International Society for Pharmaceutical Engineering (ISPE) Guide for Validation of Automated System (GAMP), or the systems engineering "V-Model" process.

operate with the minimum practical level of operator intervention.[25] As part of the control strategy, alarms should be implemented in the automation system to ensure that the system continues to operate within the predefined limits. Action taken in response to alarms should be commensurate with the severity of the triggering event. The quality unit should determine in advance the appropriate actions for specific alarms or classes of alarms, which could include, for example, operator observation, operator intervention, or automated diversion of material. Standard operating procedures (SOPs) should be established in advance for responding to and reacting to alarms or alarm classes, as well as for investigating the underlying issue that triggered the alarm.

Electronic data and data systems must comply with 21 CFR parts 11 and applicable sections of 211. Considerations applicable to electronic data may include (but is not limited to) the following:

- Accurate reproduction of the appropriate master production or control record
- Documentation that each significant step was accomplished, including but not limited to in-process results and the identification of the person checking the significant step performed by the automated equipment
- Network security, system integrity/functionality checks, single-user identification, and audit trails
- Software version control, manufacturing batch record version control, and the integrity of loaded manufacturing process during start-up
- Computing speed and capacity, local and remote memory, and communication assurance
- Data archiving and recall
- Software maintenance and change controls

The automated controls system is likely to be the primary source of batch records for batch record review of continuous processes. Data reporting and review considerations generated by the automated controls systems should include (but are not limited to):

- Manufacturing batch record: report with initial set-points and ranges and model versions
- Actions performed: audit trail (including sub-systems) reports, process parameter and in-process material attribute control charts, material collection report (documenting the conditions achieved when material was collected, diverted, or when collection commenced), and any reports from any other process-specific performance metrics
- Deviations: alarm reports, periods of material diversion, and corrective actions reports
- Materials: reconciliation and material collected, segregated and diverted report, and actual and theoretical percent yield

[25] For example, per 21 CFR 211.188(b)(11), significant steps performed by the automation must be checked by a human. As such, operator confirmation may be required for critical manufacturing steps (e.g., confirmation of the start of product collection once a state of control has been established).

C. Process Validation

The guidance for industry *Process Validation: General Principles and Practices* and *ICH Q8, Q9,* and *Q10,* is applicable to continuous manufacturing processes. For these types of manufacturing processes, the ability to evaluate real time data to maintain operations within established criteria to produce drug products with a high degree of assurance of meeting all the attributes they are intended to possess is an integral element of process validation. Manufacturers using continuous manufacturing processes may find that some process validation stages are more concurrent and interrelated (e.g., process design and equipment qualification) than they are with batch manufacturing processes. This is, in part, because the development of a continuous manufacturing process generally uses commercial scale equipment. This offers significant advantages in that equipment size scale-up issues commonly encountered in the development of batch manufacturing processes will likely be minimized. Consequently, there may be activities described below in stages 2 and 3 that may be more appropriate to perform during stage 1. For example, it may be more appropriate to perform some equipment qualification activities prior to some stage 1 validation studies as those studies may also be used to demonstrate inter- and intra-batch variability at commercial scale (i.e., during process performance qualification (PPQ)). That is, it is important to ensure that the equipment operates properly prior to generating data that satisfies some of the expectations for PPQ. Furthermore, to better understand inter- and intra-batch variability, the design of the process monitoring strategy during development should consider monitoring needs for commercial scale continued process verification throughout the life cycle of the product (stage 3).

1. Stage 1 – Process Design

Stage 1 process design includes designing the process and establishing the control strategy. The corresponding studies and decision points, including the design of equipment and automation systems, assessment of input material attributes, process dynamics and variability, development of strategies or procedures for material diversion, process monitoring and control, and other control strategy elements, have already been discussed in section III.B. This development provides a foundational understanding of the manufacturing process and quality expectations for operation and is essential for enabling verification of process robustness in stage 2.

2. Stage 2 – Process Qualification

Qualification of the integrated equipment and automated control systems is essential for ensuring the performance of a continuous process. Given the interrelated nature of the integrated equipment, process design, and control strategy, the first component described in stage 2 of the *Process Validation* guidance, Design of Facilities and Qualification of Utilities and Equipment, may often be more appropriate to perform in stage 1. Additionally, information on the equipment and automation system performance and its variability will inform the design of the PPQ protocol. Because the reliable performance of equipment and automation is critical for PPQ, manufacturers should evaluate whether they have sufficient experience with the fully integrated continuous manufacturing process before initiating PPQ.

The second part of stage 2 PPQ demonstrates the robustness of the manufacturing process and adequacy of the control strategy following completion of process development and integrated equipment-automation qualification. The PPQ protocol should be designed to assess robustness with respect to the known sources of variability including those unique to continuous manufacturing processes (e.g., mass flow rate fluctuation from a loss-in-weight feeder) and should leverage knowledge gained from Process Design and Equipment Qualification.

PPQ should also demonstrate the reproducibility of the manufacturing process over time (from start-up to shutdown and from batch to batch), and therefore manufacturers should establish measures of process stability and associated acceptance criteria as part of the PPQ protocol. Equipment performance criteria can be established to identify equipment problems and deviations that would impugn the adequacy of the equipment design or qualification, versus those that result from common cause variations. Metrics should be established to assess process robustness (e.g., parameter stability/variance and the actual yield).

The design of the initial PPQ study to examine a run time or manufacturing period should be representative of the intended commercial run time for the initial product launch. An integrated continuous manufacturing process may encounter unforeseen sources of variability with extended run times, such as process drift, equipment fatigue, and material buildup. Stage 1 process understanding and control strategy design and stage 2 equipment qualification experience can be leveraged to demonstrate that the proposed PPQ run time is sufficient to accurately capture expected process variability and therefore demonstrate intra-batch process robustness. Likewise, for processes that are expected to run in campaigns (i.e., consecutive batches), PPQ should be designed to capture variability associated with campaigning and may also leverage stages 1 and 2 understanding of these manufacturing extensions, as needed. In later stages of the product life cycle, additional PPQ studies may be performed to support greater flexibility in the batch size to enable patient demand to be met more effectively.

Sampling plans (online, at-line, or offline) for critical intermediate or finished product quality attributes during PPQ should be sufficient to verify that consistent quality material is being produced throughout the run. The magnitude and duration of variability for process parameters and quality attributes should be evaluated as part of the PPQ protocol, and should be justified. For batch processes, PPQ will generally have a higher level of sampling, additional testing, and greater scrutiny of process performance than would be typical of routine commercial production. Continuous manufacturing processes using high frequency monitoring of process parameters and quality attributes may not need additional monitoring during PPQ.

PPQ should include interventions which would normally occur during the process (e.g., PAT probe replacement at pre-established intervals, feeder refills, or shift changes). If disturbances do occur during PPQ, the PPQ study should confirm that the automated system, operations, and the quality unit are capable of identifying the event, diverting material, and/or making process corrections, as intended and per established procedures.

3. Stage 3 – Continued Process Verification

Continued process verification (CPV) provides continual assurance that the process remains in a state of control during commercial manufacture. The routine utilization of in-line, on-line, or at-line measurements employed in continuous manufacturing processes facilitates the ability to gather, analyze, and trend product and process data.

CPV encompasses an ongoing program to collect and analyze product and process data that relate to product quality.[26] The data collected should include relevant process parameters, equipment performance indicators, and quality attributes of input materials, in-process material(s) and finished product. Data analysis and trending should include:

- Quantitative and statistical methods, including multivariate approaches, whenever appropriate and feasible;
- Scrutiny of intra-batch as well as inter-batch variation; and
- The development, implementation, evaluation, and improvement, as necessary, of a plan for the frequency of analysis, attributes for examination, and predetermined statistical criteria for variance.

The product and process knowledge gathered through data analysis and trending should be used to facilitate continued process verification, initiate process improvements (e.g., refining the control strategy), and support postapproval changes.

D. Additional Pharmaceutical Quality System Considerations

To implement continuous manufacturing in an existing manufacturing facility, the site should evaluate its PQS and associated elements to determine if the design and programs within the PQS should be modified. For example, revised or additional procedures may need to be adapted or established to support a continuous manufacturing process, including:

- Handling of planned and unplanned process disturbances which occur real-time, including the associated investigations
- Raw and in-process material investigations
- In-process material diversion strategy, including the criteria for rejection of the entire batch
- Change management and maintaining an effective corrective action and preventive action (CAPA) system
- PPQ protocol and continued process verification approach, including process robustness, actual yield, and multivariate tracking and trending
- Equipment qualification and maintenance
- Use of formal and informal quality risk management principles throughout manufacturing operations and quality decision-making

[26] See 21 CFR 211.180(e).

These PQS considerations may need to be implemented during development to support knowledge management, development of the control strategy and monitoring plan, and process validation activities.

The manufacturing site should establish an appropriate level of continuous manufacturing expertise in the quality, pharmaceutical development, manufacturing operations, equipment/engineering support, and regulatory affairs organizations.[27] It is likely that additional training would be needed. Where additional training in continuous manufacturing operations is needed, this training should be sufficient to enable each group to make decisions based on science, risk, and quality principles.

An integrated team approach for many aspects of quality unit decision-making is recommended as the design and implementation of a continuous manufacturing process is a multi-disciplinary undertaking. For example, both the quality unit and technical development functions should provide input on the design of diversion points for nonconforming material and SOPs for adjusting continuous operations following disturbances.

E. Scale-Up

In a typical batch process, scale-up is associated with an increase in equipment size. Continuous manufacturing processes offer several different modes of scale-up as discussed below. Each method of scale-up should be carefully examined to identify risks, studies to be conducted to ensure that the risks are adequately mitigated, and data needed to support the scale-up plan.

An advantage of continuous manufacturing is that the equipment used for process development can be used for commercial manufacturing. When the same equipment is used, a scale increase can be achieved by the following methods:

a. Increasing run time with no change to the mass flow rate – this is usually the simplest form of scale-up for continuous processes as it requires little change to be made to the manufacturing process. The risks associated with this method are usually related to the operation of integrated equipment, analytical instrumentation and computer systems (e.g., data storage) over longer periods of time, as well as cleaning. Equipment "dead zones," material build up, equipment drift, and transient disturbances that were not observed over shorter run times may become visible with run time increases.

b. Increasing the mass flow rate – a change in the mass flow rate results in a change to the process dynamics and residence time distribution. Hence, many aspects of the process, such as process parameters and controls, sampling frequency and size, material traceability, designated quantity for rejection following a disturbance, batch specific automation instruction files, and process limiting factors should be evaluated and adjusted, as appropriate.

[27] These considerations remain applicable when establishments choose to use contract manufacturing organizations.

c. Increasing both run time and mass flow rate – the risks associated with both (a) and (b) would apply.

An increase in scale could also be achieved by a scale-out approach where two or more units of the same equipment are run in parallel. This approach to scale-up may be appropriate when large increases in scale are desired, or when equipment used for certain unit operations tend to form bottlenecks due to comparatively long residence times. Challenges with this approach may include maintaining uniform flow distribution among the parallel units (e.g., reactors), data acquisition and storage, and material traceability.

Some continuous processes may scale-up by increasing equipment size, like a batch manufacturing process. Engineering principles of scale-up should be carefully applied, such as manufacturing process controls, sampling, traceability, and material diversion buffer at scale.

1. PQS Oversight

An effective PQS ensures that manufacturing changes, such as an increase in run time or other methods of scale-up, are appropriately evaluated by the facility's change management program.[28] Existing product and process understanding should be leveraged in evaluating change to determine the suitability of the change, adequacy of the control strategy, residual risks and associated mitigation strategy, and what type of new validation studies are necessary to plan and execute to support the change. These changes may be evaluated during an onsite inspection.

2. Postapproval Filing Strategies for Scale-Up

For an application product, one element of the change control is to determine an appropriate postapproval filing strategy based on the potential to impact the quality of the finished product and complexity of the change. A submission should include sufficient details on how the scale-up would be evaluated, including testing and sampling, acceptance criteria, and the number of runs supporting the change. Comparability protocols may also be useful for scale-up for application products (e.g., flow rate changes). As the complexity of the change may have a significant potential to impact the quality of the finished product, prior discussion with the Agency may be useful.[29]

An increase in batch size by increasing only the run time with no changes to the approved manufacturing process, ranges, and equipment, is the most straightforward type of scale-up for continuous manufacturing processes, but still involves risks as noted above. Firms with a robust PQS and either experience with the subject product's continuous manufacturing process or experience with other suitably similar continuous manufacturing processes, may be able to

[28] The elements of a robust change management program are described in guidance for industry *Quality Systems Approach to Pharmaceutical CGMP Regulations* (September 2006) and guidance for industry *ICH Q10 Pharmaceutical Quality* (April 2009).

[29] Refer to guidance for industry *Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization* (September 2016).

manage the scale-up via an increase in the run time by the facility's PQS without a supplement or comparability protocol.

F. Stability

Regulatory expectations for demonstrating adequate stability over the finished drug product's shelf life do not change between batch manufacturing and continuous processing. However, there are some differences that should be considered when developing the stability plan.

As described in guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products,* data from stability studies should be provided on at least three primary batches of the drug product, and where possible, these should be manufactured by using different batches of the drug substance. An applicant may take this approach when preparing a drug application using a continuous manufacturing process. Primary stability batches may be produced from shorter manufacturing runs, provided that a state of control is established and maintained when the process operates over the longer run times. Alternatively, stability samples could be obtained from a single continuous manufacturing campaign where manufacturing variability is captured (e.g., by introducing different batches of input material(s) in a sequential manner). If this latter approach is used, the stability samples should be collected to capture this variability.

G. Bridging Existing Batch to Continuous Manufacturing

There may be situations where a continuous manufacturing process is proposed in a regulatory submission while a different process, such as a batch process, is used to make the clinical, bioequivalence, registration stability, or commercial batches. A company may also wish to introduce a continuous process at the later stage of development or as a postapproval manufacturing change.

A change from batch to continuous manufacturing is a change in the scientific operating principle, and it likely results in changes in many aspects of product and process design, such as equipment, process parameters, and control strategy. Therefore, the most appropriate filing strategy for a postapproval change to a continuous manufacturing process usually would be a prior approval supplement (PAS). A discussion with the Agency of the proposed change and the bridging strategy is encouraged to gain feedback prior to conducting the studies.[30]

An evaluation of the transition from batch to continuous manufacturing should include a comparison of individual unit operations, process parameters, equipment, CQAs, and the control strategy. In the cases where the continuous process may be based on the same unit operations and formulation as used for the batch process, the risk of change to product quality attributes (e.g., polymorphic form, dissolution, impurities, and stability) may be low and demonstration of in vitro equivalence may be sufficient to support such a change. Demonstration of in vitro equivalency may be supported by comparative batch data, including (not limited to) physicochemical properties (e.g., polymorphic form and particle size), impurity profiles, drug release profiles, and bridging stability data. However, there could be cases in which significant

[30] See footnote 29.

changes or novel approaches are used in switching from a batch to continuous manufacturing process. For example, the continuous process could incorporate a novel crystallization method that changes crystal form or a formulation change. These changes could pose a higher risk, and therefore may warrant additional in vivo bioequivalence studies. As these changes may impact safety, efficacy, and other aspects of an approved product, prior discussion with the Agency is recommended.[31]

IV. LOCATION OF INFORMATION IN AN APPLICATION

Information within submissions to FDA should be submitted in the Common Technical Document format in accordance with guidance for industry *M4Q: CTD – Quality*. Enhanced process development approaches should be provided as described in guidance for industry *Q8(R2) Pharmaceutical Development*. The table below provides recommendations for placement of information unique to continuous manufacturing (e.g., RTD) for drug product that may not be addressed in these documents.[32] The table is not a comprehensive list of the data requirements for a continuous manufacturing application; the application should contain all relevant information as required by 21 CFR part 314. Although not required, submission of an overview document to facilitate navigation may be helpful.

Recommendations for placement of information unique to continuous manufacturing

Information and Data	**eCTD Location for Drug Products**
Pharmaceutical Development	
• Suitability of the proposed material attributes of raw materials, excipients, and drug substance for continuous feeding and manufacturability	3.2.P.2.1

[31] See footnote 29.

[32] For the end-to-end continuous manufacturing process, the sponsor/applicant should consult with the Agency regarding the placement of information unique to this type of continuous manufacturing design prior to the NDA or ANDA submission.

Information and Data	**eCTD Location for Drug Products**
• Characterization of the process dynamics for the integrated system using a suitable scientific approach (e.g., RTD studies). Recommended information: ▪ A description of the method or approach used to characterize the process dynamics ▪ A science- and risk-based evaluation of the factors (material attributes, process parameters, equipment configuration) that may impact the process dynamics For RTD data: Representative RTDs reflecting routine commercial production conditions (e.g., grade of materials, mass flow rates, material transfer connections, and equipment). Characterization of the RTDs for mean residence time and shape of the distribution using a suitable measure, such as mean centered variance, standard deviation, or characteristic times (e.g., t_{10} and t_{90} or t_5 and t_{95}).	3.2.P.2.3 3.2.P.4
• Product and process characterization during normal operation and planned transient operations (e.g., start-up, shutdown)	3.2.P.2.3
• Material traceability strategy • Material collection and diversion strategy, including: ▪ Justification for product collection ▪ Potential events that trigger material diversion ▪ The rationale for selection of the amount of material to be diverted (e.g., impacted material based on RTD and material traceability) ▪ Description of the current criteria for rejection of the entire batch	3.2.P.2.3
• Development data to support the proposed mass flow rate, run time, and process parameters and ranges.	3.2.P.2.3
• Supporting information for PAT and model development • Justification of finished product sampling strategies, including any backup methods when PAT device is unavailable	3.2.P.2.3
• Supporting information and rationale for advanced process control approaches (e.g., feedback, feedforward, model predictive), including identification of the controlled and manipulated parameters	3.2.P.2.3
Manufacture	
• Definition of batch size, including proposals for batch size ranges	3.2.P.3.2

Information and Data	eCTD Location for Drug Products
• Process flow diagram with sufficient detail to describe continuous flow operational aspects. Elements which should be included are, among other things: ▪ Material flow including hold up steps and recycle loops ▪ Rejection and/or diversion points ▪ Critical process parameter ranges; design space (if applicable) ▪ In-process controls, sampling and PAT locations ▪ Advanced process controls used (e.g., feedback control)	3.2.P.3.3
• Justification of sampling strategies for finished product testing, including any backup methods when PAT device is unavailable • Development and supporting data for PAT methods and models	3.2.P.3.4
• Description of advanced process control approaches (e.g., feedback, feedforward, model predictive)	3.2.P.3.4
Control of Drug Product	
• PAT methods used for release, including RTRT methods: ▪ Description of primary and alternate methods ▪ Description of the statistical analysis of data ▪ For submission of NIR based spectroscopic PAT methods, refer to guidance for industry *Development and Submission of Near Infrared Analytical Procedures* ▪ For submission of model based methods, refer to guidance for industry *Q8, Q9 & Q10 Questions and Answers* | Appendix Q&As from Training Sessions	3.2.P.5
• Summary of the control overall strategy	3.2.P.5.6

V. DEFINITIONS

Active Process Control System: A system consisting of hardware and software architecture, mechanisms, and algorithms that automatically adjusts a process to maintain the process output within a desired range.

Automation System: A broad range of systems to monitor and control the production of goods and services. The automated system can refer to computer hardware, software, peripheral devices, networks, cloud infrastructure, operators, and associated documents (e.g., user manuals and standard operating procedures).[33]

[33] Refer to International Society for Pharmaceutical Engineering's Good Automated Manufacturing Practice Good Practices Guides and guidance for industry *Data Integrity and Compliance with CGMP* (December 2018).

Batch: A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits and is produced according to a single manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2)).

Continuous Manufacturing: An integrated process that consists of a series of two or more unit operations ("the system"). In such a process, the input material(s) are continuously fed into and transformed within the process, and the processed output materials are continuously removed from the system.

Although the amount of material being processed at any given instance may be relatively small in a continuous manufacturing process, the process can run over a period of time to generate necessary quantities of finished material with the desired quality in response to the market demand. There are different integration approaches for continuous pharmaceutical manufacturing processes. In an end-to-end approach, the drug substance and drug product process steps are fully integrated into a single continuous process and there is no isolated drug substance or intermediate. In a hybrid approach, a combination of batch and continuous process steps are used for drug substance or drug product manufacture.[34]

Control Strategy: A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (*ICH Q10*).

Continued Process Verification: Assurance that during routine production the process remains in a state of control.[35]

Disturbance: A change to the input to the process (e.g., process parameter, material property, equipment condition, and/or environment) that is either intentionally or unintentionally introduced into the system.[36]

Lot: A batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that assures its having uniform character and quality within specified limits (21 CFR 210.3(b)(10)).

Pharmaceutical Quality System (PQS): Management system to direct and control a pharmaceutical company with regards to quality (*ICH Q10*).

[34] In the hybrid approach, a drug manufacturer may implement continuous manufacturing for portions of a process, or for an entire process.

[35] See guidance for industry *Process Validation: General Principles and Practices* (January 2011).

[36] Adapted from Riggs JB (1999) Chemical Process Control, Lubbock, TX: Ferret Publishing.

Real Time Release Testing: The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls (*ICH Q8*).

Residence Time Distribution (RTD): A probability distribution that describes the amount of time a mass or fluid element remains in a process.[37]

State of Control: A condition in which the set of controls consistently provides assurance of continued process performance and product quality (*ICH Q10*).

Transient States: Conditions where the process goes through dynamic period and a change happens over time. This change may be due to either disturbances or intentional alterations in the selected operating conditions.

VI. REFERENCES

Allison G, YT Cain, C Cooney, T Garcia, TG Bizjak, O Holte, N Jagota, B Komas, E Korakianiti, D Kourti, R Madurawe, E Morefield, F Montgomery, M Nasr, W Randolph, JL Robert, D Rudd, D Zessa, 2014, Regulatory and quality considerations for continuous manufacturing, May 20-21, 2014, Continuous Manufacturing Symposium, J Pharm Sci, 2015;104(3):803-812.

European Medicines Agency Guideline on Real Time Release Testing (October 1, 2012), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125401.pdf (accessed on October 4, 2018).

International Society for Pharmaceutical Engineering Good Automated Manufacturing Practice (GAMP) Good Practice Guides, www.ispe.org.

Kourti, T, J Lepore, L Liesum, M Nasr, S Chatterjee, CMV Moore, et al., 2014, Scientific and Regulatory Considerations for Implementing Mathematical Models in the Quality by Design (QbD) Framework, Pharmaceutical Engineering, 34(6):1-21 (Published November/December 2014) (Online Exclusives) (accessed on October 4, 2018) (https://ispe.org/sites/default/files/pe/online-exclusives/14ND-online_Kourti.pdf).

Nasr, M, M Krumme, M Yoshihiro, L Trout Bernhardt, C Badman, S Mascia, CL Cooney, KD Jensen, A Florence, C Johnston, K Konstantinov, SL Lee, 2017, Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving from Theory to Practice: September 26-27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals, J Pharm Sci, (https://doi.org/10.1016/j.xphs.2017.06.015).

[37] Nasr, MM, et. al., *Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving From Theory to Practice.* September 26-27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals. J Pharm Sci. (Epub ahead of print).

Guidances for Industry[38]

Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization (September 2017)

Data Integrity and Compliance with Drug CGMP: Questions and Answers (December 2018)

Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products (May 2015)[39]

M4Q: The CTD – Quality (August 2001)

PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (September 2004)

Process Validation: General Principles and Practices (January 2011)

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (December 2000)

Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (August 1999)

Q8, Q9 & Q10 Questions and Answers | Appendix Q&As from Training Sessions (July 2012)

Q8(R2) Pharmaceutical Development (November 2009)

Q9 Quality Risk Management (June 2006)

Q10 Pharmaceutical Quality System (April 2009)

Quality Systems Approach to Pharmaceutical CGMP Regulations (September 2006)

[38] Guidances are available at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.
[39] Ibid.