Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products

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DRAFT GUIDANCE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)
Center for Biologics Evaluation and Research (CBER)

May 2015
Pharmaceutical Quality/CMC

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Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products 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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 create 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 has been developed to address the lack of clarity with respect to what chemistry, manufacturing, and controls (CMC) information in a marketing application constitutes an established condition or a "regulatory commitment" that, if changed following approval, requires reporting to FDA. Clarification regarding which elements of the CMC information constitute established conditions and where in an application these elements are generally expected to be described, should lead to a better understanding that certain CMC changes can be made solely under the Pharmaceutical Quality System (PQS)[2] without the need to report to FDA. For those changes that do require reporting, a better understanding of established conditions could allow for a more effective post-approval submission strategy by the regulated industry.

Specifically, this guidance describes those sections in a common technical document (CTD)-formatted application that typically contain information that meets the definition of established conditions, and provides considerations for managing and communicating changes to the approved established conditions over the lifecycle of an approved product.

This guidance is intended for applicants[3] submitting original new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs) to CDER and CBER.[4]

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

[2] As described in the guidance for industry *Q10 Pharmaceutical Quality System* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf), a Pharmaceutical Quality System (PQS) is defined as a management system to direct and control a pharmaceutical company with regard to quality. (The definition in the International Conference on Harmonisation (ICH) Q10 is based upon International Standards Organisation (ISO) 9000:2005).

[3] In this context, the use of the term "applicant" assumes that an applicant is both a manufacturer and the application holder. Any description of manufacturing and control practice recommendations or references to existing requirements are generally intended for the manufacturer, if separate from the applicant. When application

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

The regulations at 21 CFR 314.50(d)(1) and 314.54(a)(1) require that any NDA or ANDA submitted to the Agency contain a CMC section that describes information such as the composition of the drug product, manufacture of the drug substance, and manufacture of the drug product. Similarly, under 21 CFR 601.2, applicants submitting BLAs must also provide relevant CMC information, such as a full description of manufacturing methods and data establishing stability of the product through the dating period.

All changes after approval of an application must be managed and executed in conformance with current good manufacturing practices (CGMP), although 21 CFR 314.70(a) and 601.12(a) only require a subset of changes to be reported to the FDA. 21 CFR 314.70(a)(1)(i) states that, other than the exceptions or alternatives provided in 21 CFR 314.70(a)(1)(ii), an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in an application (i.e., an NDA or ANDA). Per 21 CFR 601.12(a)(1), an applicant must inform FDA about each change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved license application (BLA).

After approval of an application, applicants desiring to make changes to this CMC information must evaluate the changes in the context of the regulations in order to determine if there is a need to report the change and associated supporting data and justifications to FDA.

However, there has not been a common understanding of the meaning of the phrases "each condition established in an approved application" and "established in the approved license application(s)." The practical meaning of these phrases has been described in many ways since the revision of the post-approval change regulations as part of the Food and Drug Administration Modernization Act (FDAMA) in 1997.[5] In recent communications, these phrases have been used synonymously with the term "regulatory commitments" by both the regulated industry and the FDA. In this guidance, the phrases "conditions established in an approved application" and changes "established in the approved license application(s)" are referred to as established

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submission expectations are described, FDA expects these to be followed by the applicant working with any listed contracted manufacturing site(s), and in coordination with the contract manufacturer's PQS.

[4] This guidance is not applicable to whole blood, blood components, and plasma. Also, it is not applicable to biological products that meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)), or Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) regulated solely under section 361 of the Public Health Service Act.

[5] See the Food and Drug Administration Modernization Act (Public Law 105-115).

conditions, instead of "regulatory commitments" as there are varying interpretations of the term "regulatory commitment."

FDA guidance documents, such as those listed below,[6] clarify the recommended reporting mechanism (i.e., supplement, annual report) for post-approval CMC changes.[7]

- SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (11/1/1995)
- Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (7/1/1997)
- Changes to an Approved Application: Biological Products (7/1/1997)
- Changes to an Approved NDA or ANDA (4/1/2004)
- CMC Post-approval Manufacturing Changes To Be Documented in Annual Reports (3/14/2014)

Although the reporting mechanism for many CMC changes is clear, FDA is concerned that there is confusion regarding which elements of an application are considered to be established conditions. This confusion could have a negative impact on change management activities and could discourage continual improvement in product manufacturing processes, lead to unnecessary submission of post-approval supplements to FDA for changes that could be managed solely by a manufacturer's PQS, or, upon inspection, lead to Form 483 observations for changes that should have been reported to FDA. The recommendations in this guidance pertaining to submission of information about established conditions in original applications, supplements, and annual reports are intended to increase clarity and transparency and help avoid such potentially negative outcomes.

Moreover, a better understanding of which elements of the CMC information constitute established conditions to FDA, and where in an application these elements are generally expected to be described, could allow for a more effective post-approval submission strategy (e.g., effective use of risk management principles in ICH Q9, and knowledge management[8] as defined in ICH Q10) by the regulated industry. Clarity on what constitutes an established condition will also provide FDA with pathways to better regulate post-approval changes by utilizing more flexibility and risk-based principles, as envisioned by the pharmaceutical product

[6] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[7] As part of a periodic evaluation of the available guidances, FDA will be reviewing all relevant change management guidances to ascertain if any revisions need to be made. We recommend contacting the appropriate CDER or CBER review division to ensure that the referenced guidance still represent FDA's current thinking.

[8] Knowledge management as defined in ICH Q10 is a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components.

quality initiatives laid out by FDA's *Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century – A Risk Based Approach (September 2004).*[9]

Additionally, better clarity regarding what parts of an application are established conditions might support a future approach in which an applicant could rely upon one or more robust PQSs to assess, validate, and implement many post-approval changes appropriately, resulting in a more systematic reduction in or elimination of certain reporting requirements. Future guidance may be developed to further support such an approach.

III. ESTABLISHED CONDITIONS

A. Definition of Established Conditions

FDA defines established conditions as the description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure process performance and quality of an approved product. Changes to the established conditions must be reported to FDA (21 CFR 314.70 and 601.12).

See section IV.A of this guidance for more specificity regarding what CTD sections[10] of the Quality (CMC) portion of the application generally contain established conditions. Sufficient detail should be provided in the application regarding the proposed established conditions to assure process performance and quality of the approved product. For example, a manufacturing process description must be submitted in accordance with the appropriate regulations (i.e., 21 CFR 314.50(d)(1)(ii)(c), 314.94, and 601.2). If insufficient detail is provided to determine the established conditions, this will be addressed during application review. Failure to provide sufficient detail in the application could delay review, and preclude approval, of the submission.

B. Elements of a Control Strategy that May Be Considered Established Conditions

The term control strategy is used in the definition of established conditions. ICH Q10 describes a control strategy as a planned set of controls, derived from current product and process understanding, that assures process performance[11] and product quality. The controls can include parameters and attributes related to drug substance (DS), excipients, in-process materials, drug product (DP) materials, inclusive of small and large molecule products, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring, sampling, testing, and control, etc.

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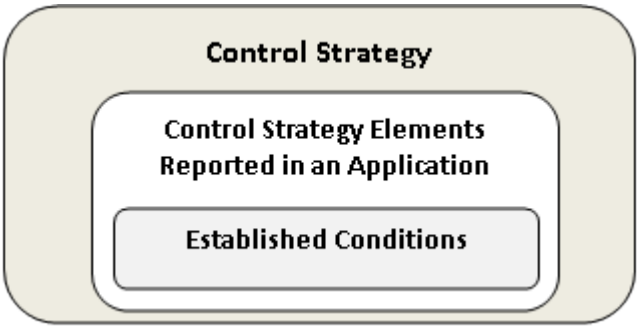
[9] For more information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/QuestionsandAnswersonCurrentGoodManufacturingPracticescGMPforDrugs/UCM071836.

[10] Our definition of established conditions is consistent with the submission structure described in the ICH M4Q-CTD guidance for the Quality (CMC) portion of an application submitted to FDA. See ICH guidance for industry on *M4Q: The CTD — Quality.*

[11] For the purposes of this guidance, "process performance" refers to the ability of the process to reliably produce a quality product.

Currently there are elements of an overall control strategy that may not be included in a submission and may be managed solely under the PQS. This guidance is not expanding the definition of control strategy, with respect to submission expectations (see diagram below). The intent of this guidance is to clarify which elements of the control strategy ***that are submitted in an application*** may be considered established conditions. For this purpose, control strategy elements, that could be established conditions described in an application, may include, but are not limited to, the following:

- DS/DP (including in-process materials) manufacturing[12] and testing facilities.
- Source of and specifications for starting materials for biological products.
- Process, including in-process tests and sequence of operations, equipment; and process parameters and their ranges.
- Specifications, including the tests, analytical procedures and acceptance criteria; including specifications for the DS, other components, in-process materials, and the DP.
- Container closure system, components, and specifications.
- Maintenance strategy for chemometric and/or multivariate models (e.g., for models that may have a high impact on product quality).



Based on current review practices, for complex products (including many biological and biotechnology products) and other difficult-to-characterize products, the level of product and process knowledge, ability to accurately assess risk, and detection of deleterious impact from process changes can be more challenging to determine. In these cases, FDA will consider these aspects when assigning allowable variations within the established conditions in the application.

There also may be instances where the relevance of the established conditions will depend on manufacturing site specific capabilities, such as on-line, real-time attribute monitoring. Therefore, certain elements of established conditions may need to be specific to a particular

[12] For drug products, *manufacture, processing, packing, or holding of a drug product* includes packaging and labeling operations, testing, and quality control of drug products, see 21 CFR 210.3(12).

facility or facilities should the application have multiple facilities approved for the same intended function (e.g., two commercial manufacturing sites using different processes).

Although a control strategy is generally supported and verified by elements listed below, these elements are not generally considered established conditions:

- Batch records[13]
- Development data
- Characterization data
- Validation data[14]
- Batch analysis data[15]

A product control strategy initially provided in the application should reflect current product and process understanding. This implies that the control strategy for a given product can evolve and be updated as knowledge is gained and additional risk management activities occur throughout the product's life cycle (see section IV.B. for more information).

IV. PRINCIPLES FOR ESTABLISHED CONDITIONS IN APPLICATIONS

A. Sections of CTD That Typically Contain Established Conditions

The following table identifies those sections of a CTD-formatted application that typically contain information that FDA considers to meet the definition of established conditions, as provided in section III of this guidance. This table is intended as a guide to assist the applicant and FDA in identifying established conditions. The relevant information would still be considered an established condition even if it is located in a CTD section not specified below.

[13] The batch record should reflect the current manufacturing process and the associated in-process parameters and controls needed to ensure product quality and performance. It is not expected that all changes to a batch record would be reported to FDA, but if there is a change to the control strategy that impacts the batch record, a current batch record should be provided in the appropriate regulatory submission. Refer to 314.50(d)(1)(ii)(c) and 314.94(a)(9) for associated regulations about batch record submission.

[14] Process validation activities are not considered established conditions per this guidance; however, validation activities are still expected to support approved manufacturing processes and analytical methods, and any changes to manufacturing processes and approved analytical methods should be supported by validation activities, as appropriate. Note that process validation data and/or other clinical and/or nonclinical laboratory studies are required to be reported for changes to biological products (see 21 CFR 601.12(a)(2)).

[15] Batch analysis data are not considered established conditions. For example, batch analysis data are the output of the specification (i.e., test, analytical method, and acceptance criteria) used to assure and verify that the desired performance and quality are achieved.

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CTD SECTION	SECTION TITLE	Contains Established Conditions[16]	Examples of Established Conditions (not an all-inclusive list)
3.2.S	**DRUG SUBSTANCE**		
3.2.S.1	**General Information**		
3.2.S.1.1	Nomenclature	X	Established Name or Proper Name (for Biologics)
3.2.S.1.2	Structure	X	For a New Chemical Entity: Structure of the drug substance, including stereochemistry, molecular formula, molecular mass For Biotech Products: Schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass
3.2.S.1.3	General Properties		
3.2.S.2	**Manufacture**		
3.2.S.2.1	Manufacturer(s)	X	Name, address, manufacturing steps and/or type of testing, and responsibility
3.2.S.2.2	Description of Manufacturing Process and Process Controls	X	Sequential procedural narrative, including certain information in the control strategy that assures process performance and drug substance quality, such as: identification of steps, process controls and parameters (with ranges), equipment and operating conditions (including target settings), input materials, and intermediates.
3.2.S.2.3	Control of Materials	X	Material specifications (tests, analytical procedures and acceptance criteria) For Biologicals: Source of materials (e.g. cell and seed source, raw materials) and specification of materials (e.g., tests, analytical procedures and acceptance criteria)

[16] Elements that are not identified in an approved application as being established conditions are considered parts of an application that would not require reporting to FDA if postapproval changes were made, as defined in this guidance. However, if there is a change to an established condition, which by definition requires reporting (e.g., adding a new analytical procedure or substantially modifying an existing analytical procedure), these supportive elements (e.g., validation data, batch analysis) should be submitted to support the change.

CTD SECTION	SECTION TITLE	Contains Established Conditions[16]	Examples of Established Conditions (not an all-inclusive list)
3.2.S.2.4	Controls of Critical Steps and Intermediates	X	Critical process steps: Tests and acceptance criteria that are part of the overall control strategy (including microbial control strategy) Intermediates (e.g., isolated intermediates): Specifications (tests, analytical procedures and acceptance criteria) and hold times
3.2.S.2.5	Process Validation and/or Evaluation		
3.2.S.2.6	Manufacturing Process Development		
3.2.S.3	**Characterization**		
3.2.S.3.1	Elucidation of Structure and other Characteristics		
3.2.S.3.2	Impurities		
3.2.S.4	**Control of Drug Substance**		
3.2.S.4.1	Specification	X	Drug substance specifications (tests, analytical procedures and acceptance criteria)
3.2.S.4.2	Analytical Procedures	X	Parameters and criteria for analytical procedures for drug substance specifications that are part of the overall control strategy
3.2.S.4.3	Validation of Analytical Procedures		
3.2.S.4.4	Batch Analyses		
3.2.S.4.5	Justification of Specification		
3.2.S.5	**Reference Standards or Materials**	X	Qualification protocols for new and existing reference standards or materials

CTD SECTION	SECTION TITLE	Contains Established Conditions[16]	Examples of Established Conditions (not an all-inclusive list)
3.2.S.6	**Container Closure System**	X	Selected container closure system and controls
3.2.S.7	**Stability**		
3.2.S.7.1	Stability Summary and Conclusions		
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	X	Tests, analytical procedures and acceptance criteria; storage conditions; shelf life; post-approval testing protocol; and commitment(s)
3.2.S.7.3	Stability Data		
3.2.P	**DRUG PRODUCT**		
3.2.P.1	Description and Composition of the Drug Product	X	Description and composition for each strength including list of components, quality standard for the components (e.g., USP or NF), grade , amount of each in the formulation, function of the components in the product Note: This also includes a description of accompanying diluents or devices
3.2.P.2	**Pharmaceutical Development**		
3.2.P.2.1	Components of the Drug Product		
3.2.P.2.1.1	Drug Substance		
3.2.P.2.1.2	Excipients		
3.2.P.2.2	Drug Product		
3.2.P.2.2.1	Formulation Development		
3.2.P.2.2.2	Overages		
3.2.P.2.2.3	Physicochemical and Biological Properties		
3.2.P.2.3	Manufacturing Process Development		
3.2.P.2.4	Container Closure System		
3.2.P.2.5	Microbiological Attributes		
3.2.P.2.6	Compatibility		
3.2.P.3	**Manufacture**		

CTD SECTION	SECTION TITLE	Contains Established Conditions[16]	Examples of Established Conditions (not an all-inclusive list)
3.2.P.3.1	Manufacturer(s)	X	Name, address, manufacturing steps and/or type of testing, and responsibility
3.2.P.3.2	Batch Formula	X	Commercial scale batch formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls	X	Sequential procedural narrative, including certain information in the control strategy that assures process performance and product quality, such as: identification of steps, process controls and parameters (with ranges), equipment and operating conditions (including target settings), input materials For products purporting to be sterile, the control strategy should include details regarding the product or component sterilization methods and/or aseptic manufacturing operations
3.2.P.3.4	Controls of Critical Steps and Intermediates	X	Critical process steps: Tests and acceptance criteria that are part of the overall control strategy (including microbial control strategy) Intermediates (e.g., in-process blend): Specifications (tests, analytical procedures and acceptance criteria)
3.2.P.3.5	Process Validation and/or Evaluation		
3.2.P.4	**Control of Excipients**		
3.2.P.4.1	Specifications	X	Specifications (tests, analytical procedures and acceptance criteria) for all in-coming materials
3.2.P.4.2	Analytical Procedures	X	Parameters and criteria for analytical procedures for excipient specifications that are part of the overall control strategy
3.2.P.4.3	Validation of Analytical Procedures		
3.2.P.4.4	Justification of Specifications		

CTD SECTION	SECTION TITLE	Contains Established Conditions[16]	Examples of Established Conditions (not an all-inclusive list)
3.2.P.4.5	Excipients of Human or Animal Origin	X	List of excipients of human or animal origin, source and associated controls
3.2.P.4.6	Novel Excipients	X	List of novel excipients and associated controls
3.2.P.5	**Control of Drug Product**		
3.2.P.5.1	Specification(s)	X	Drug product specifications (test, analytical procedure and acceptance criteria)
3.2.P.5.2	Analytical Procedures	X	Parameters and criteria for analytical procedures for drug product specifications that are part of the overall control strategy
3.2.P.5.3	Validation of Analytical Procedures		
3.2.P.5.4	Batch Analyses		
3.2.P.5.5	Characterization of Impurities		
3.2.P.5.6	Justification of Specification(s)		
3.2.P.6	**Reference Standards or Materials**	X	Qualification protocols for new and existing reference standards or materials
3.2.P.7	**Container Closure System**	X	Selected container closure system and controls
3.2.P.8	**Stability**		
3.2.P.8.1	Stability Summary and Conclusion		
3.2.P.8.2	Post-approval Stability Protocol and Stability Commitment	X	Tests, analytical procedures and acceptance criteria; storage conditions; shelf life; post-approval testing protocol; and commitment(s)
3.2.P.8.3	Stability Data		
3.2.A	**APPENDICES**		

CTD SECTION	SECTION TITLE	Contains Established Conditions[16]	Examples of Established Conditions (not an all-inclusive list)
3.2.A.1	Facilities and Equipment	X	List of all facilities, including name, address, manufacturing steps and/or type of testing, and responsibility
3.2.A.2	Adventitious Agents Safety Evaluation		
3.2.A.3	Novel Excipients	X	See 3.2.P.4.6 above
3.2.R	**Regional Information**		
	Executed Batch Records		
	Method Validation Package		
	Comparability Protocols[17]	X	Dependent on the proposed change
3.3	**Literature References**		

B. Establishing Conditions as Part of the Application Submission and Review

The applicant should provide a summary of the proposed established conditions in the application. For ease of review and to facilitate identification and discussion of established conditions in the application, we recommend that the applicant's summary be provided in Module 2, section 2.3 of the CTD, Introduction to the Quality Overall Summary. We also recommend that this information be provided in a tabular format, and include a brief description or identification of the established condition, with a reference to its specific location(s) in Module 3 of the CTD (e.g., drug substance specifications, 3.2.S.4.1 Specification, page XXX), or a hyperlink, if submitted in eCTD format.

As part of the application review process, FDA will assess the proposed established conditions in conjunction with the level of product and process understanding, the applicant's risk assessment activities, and the control strategy proposed by the applicant. Demonstration of risk mitigation within the application can allow for greater operational flexibility for certain parameters typically considered established conditions. As such, those parameters may be determined to *not* be established conditions by FDA, and therefore can be changed solely within the manufacturer's PQS, and without the need for submission of a supplement or notification in an annual report. FDA will consider the established conditions to be finalized at application approval or licensure. If FDA determines that the control strategy or supporting information (e.g., risk assessment, validation information) is based upon inaccurate information or evidence that the applicant lacks the ability to adequately manage change, FDA may reassess the appropriateness of the conditions that were considered to be established conditions in the applicant's application. In the instance

[17] A Comparability Protocol (CP) (defined in 21 CFR 314.70(e) and 601.12(e)), when submitted, typically contains a proposed approach to manage changes to the proposed established conditions; once the CP is approved, it will serve as an agreement with the Agency for the applicant to either change or augment the conditions established in the approved application through a particular reporting mechanism.

of inaccurate information, the applicant should submit corrections to the application or license as soon as possible.

For legacy products for which the applicant did not submit an original application with a clear delineation of the established conditions, FDA intends to develop a process by which applicants could obtain clarification regarding established conditions.

C. Changes to Established Conditions

All change(s) to an approved product or process, whether reportable or not, should be evaluated, approved by the quality unit, and implemented using a robust change management system within the PQS, utilizing risk management approaches as outlined in ICH Q9 and product-specific knowledge management.

Applicants should use knowledge obtained during transfer, scale up, and commercial activities to improve the control strategy. During commercial manufacturing, per 21 CFR Part 211, the applicant must assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded. Recommendations for product lifecycle activities to monitor continual assurance of the validated state[18] and continual improvement principles[19] may be found in current FDA guidance. Although the established conditions, including the applicable control strategy elements, are evaluated by FDA as part of an original application, the applicant's control strategy should be updated as new knowledge is gained and/or as new risks emerge over the lifecycle of the approved product.

When new information learned during commercial manufacturing leads to the addition or modification of one or more established conditions, the applicant should provide an updated summary of the established conditions and supportive information (e.g., validation data, batch analysis) for any new or modified established conditions in a manufacturing supplement (i.e., if a supplement is needed for the modification) or the next annual report. Alternatively, if it is determined that an established condition is no longer necessary to assure process performance and quality of the product, the applicant may remove an established condition by submitting a supplement or annual report, where the submission type is based on the recommendations found in FDA regulations and post-approval changes guidance documents or in an approved protocol. The submission should clearly explain how this determination was made, including associated commercial-scale data, studies, risk assessments, new scientific knowledge used to support this determination, and the elements of the control strategy that will provide adequate or improved control. For example, if on-line, real-time attribute monitoring is implemented post-approval for a particular unit operation, it may be acceptable to designate the on-line monitoring (e.g., NIR

[18] See the guidance for industry on *Process Validation: General Principles and Practices*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.

[19] See the guidance for industry on *Q10 Pharmaceutical Quality System*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf.

analysis) as an established condition, while removing the inputs and process parameters for the unit operation from the established conditions.

For change management activities that do not require reporting to the Agency, any related risk evaluation and product-specific knowledge used to support change management decisions should be made available upon FDA request (e.g., upon site inspection, record request). Should FDA observe meaningful differences between the approved control strategy as described in the established conditions, and additional product and process understanding gained post-approval, FDA may request that an applicant update the established conditions in the application.