DRAFT

Guidance for Industry

ChromPAC

Manufacturing Chromatography Systems Postapproval Changes: Chemistry, Manufacturing and Controls Documentation

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I. INTRODUCTION

On November 21, 1997, the President signed the Food and Drug Administration Modernization Act (the Modernization Act). Section 116 of the Modernization Act amended the Food, Drug, and Cosmetic Act (the Act) by adding section 506A (21 U.S.C. 356a), which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

Under section 506A of the Act, and Section 351 of the Public Health Service Act (PHS Act), the holder of a new drug application (NDA), abbreviated new drug application (ANDA), abbreviated antibiotic application (AADA), or Biologic License Applications (BLA) must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The Act provides for four reporting categories: (1) Prior Approval Supplement (PAS), (2) Supplement – Changes Being Effected in 30 days (CBE-30), (3) Supplement – Changes Being Effected (CBE-0), and (4) Annual Report (AR). The reporting category for a change is based on the potential for the change to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or efficacy of the drug product. The changes that require prior approval are those that have a substantial potential to have an adverse effect, CBE-30 and CBE have a moderate potential to have an adverse effect, and those reported in an AR have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or efficacy of the drug product.

Regulations described in the Code of Federal Regulations (CFR) (specifically, 21CFR314.70(g) and 601.12), section 506A of the FD&C Act, various guidance documents previously issued by FDA interpreting the regulations, and the Act currently, prescribe the requirements for reporting changes for approved drugs and licensed biological products to FDA, and provide guidance on the proper reporting category. Before distributing a product made using a change, applicants are required to demonstrate, through appropriate validation and/or other clinical or non-clinical laboratory studies, the lack of adverse effect of the change on the identity, strength, quality, purity, or potency as they may relate to the safety or effectiveness of the product.

Under the regulations and guidance, an applicant can submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category (usually by one level) for specified changes. A proposed comparability protocol is submitted as a prior approval supplement, if not approved as part of the original application. FDA has recently issued guidance documents on comparability protocols for both small and large molecules. It is expected that the changes discussed in this document are of the type that may be suitable for submission in a comparability protocol.

II. PURPOSE AND SCOPE OF GUIDANCE

This document is issued to provide manufacturers with guidance on post approval changes for chromatographic manufacturing systems. Improvement of product quality, process economics, increase in production yield and/or global harmonization of operating parameters are the main reasons for introduction of chromatography system changes. The intention of the document is to provide manufacturers with increased flexibility and clarity when reporting changes to chromatographic operations in an approved manufacturing process, while ensuring patient safety, drug efficacy and quality. This document provides guidance for post-approval changes to manufacturing process chromatography systems in the production of drug substance that is used for both chemically synthesized drug products and human specified biological products as outlined in 21 CFR 601.2 (with the exception of therapeutic DNA plasmid products) regulated by the Center for Drugs Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER).

This guidance provides recommendations to sponsors of NDAs, ANDAs, AADAs, drug master files (DMFs) and BLAs who intend, during the post-approval period, to change: 1) the components or composition of the mobile phase; 2) the composition (solid support and/or moiety) of the stationary phase; 3) chromatographic loads and other operating conditions; 4) the composition of column equipment; 5) the scale-up/scale-down of the column(s); 6) addition or subtraction of columns (number of duplicate columns or process steps); and/or 7) the site of manufacture where a chromatography system is used.

This guidance provides recommendations on reporting categories under the post approval change regulations, and guidance as they relate to chromatography systems in drug substance manufacturing processes and provides recommendations on the chemistry, manufacturing and controls information that should be provided to CDER or CBER to ensure continued drug substance and drug product quality and performance characteristics. This guidance further emphasizes the necessity to compare the product derived from the modified process to the one derived from the currently approved process. This evaluation is meant to confirm that introduction of the change(s) did not alter the physico-chemical and/or biological characteristics of the product, and therefore the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety and efficacy of the drug product.

Post-approval changes to chromatography systems used in the analytical testing procedures or the manufacture of raw material/starting materials/excipients/reagents used in drug substance/drug product process are not addressed in this document.

This guidance provides for a lower reporting level for certain chromatography systems post-approval changes contingent on the applicant providing the appropriate information as outlined in this guidance. This guidance does not affect any post-approval changes other than the ones specified.

This guidance does not comment on or otherwise affect compliance or inspection documentation that has been defined by the office of Compliance or FDA's Office of Regulatory Affairs. Applicants can contact the appropriate chemistry review teams for guidance on post-approval changes not addressed in these information sources.

III. GENERAL CONSIDERATIONS

Note: Comparability is the term most commonly used for biologic molecules while equivalence is the term most commonly used for small molecules. In this guidance, the term comparability is used to describe and encompass both terms.

It is the responsibility of the manufacturer to assess to what extent the proposed chromatography change(s) has the potential to have an adverse effect on the product. A sponsor may be able to demonstrate product comparability between material made after a manufacturing change and material made before implementation of the change through different types of analytical and functional testing (including bioassays for complex biological molecules such as mAbs) described in this document. The manufacturer should fully assess the intent of the chromatography step and the strength of the analytical tests in the assessment of the impact the change will have on the product. For example, a change in a chromatography cleaning wash step may, in one instance, have little safety impact, but could be crucial if the wash step is important in the removal of adventitious agents (and in the ability to measure that removal).

In determining the types of tests needed, the extent of the manufacturing change(s) and the stage of manufacturing at which the change(s) occurs (e.g. early recovery vs. late purification) must be considered. In particular, reporting categories for a given process change may depend on whether the change occurs pre- or post-final intermediate for a synthetic chemical compound.

It is recognized that no guidance document can address every circumstance, and that this document will have limitations in addressing each manufacturer's particular case. In addition, predictions of patient safety and drug efficacy are influenced by many factors besides the manufacturing step, for example: (1) ability to fully analyze and characterize a molecule varies depending on its complexity (e.g., acetaminophen versus insulin, versus a monoclonal antibody); (2) understanding of the mechanism of action varies from product to product and disease to disease (e.g., diabetes versus rheumatoid arthritis); (3) complexity of a clinical indication (diabetes versus post-chemotherapy supportive therapy); (4) understanding of the basis of toxicity (e.g., acetaminophen overdose versus immunogenicity) and (5) physical properties in relationship to dosage form. Considering the complexity and interdependence of these factors, it is acknowledged that there are limits to providing a universal and prescriptive set of rules.

Manufacturers should provide to the FDA adequate chemical and physical (and in some cases biological) comparisons with side-by-side analyses of the "old" and "new" materials and demonstrating that the postchange material is comparable to the prechange material.

For small molecules, the impact of the manufacturing change can be evaluated in isolated intermediates following the process step in which the manufacturing modification is made. For biotechnology-derived products, comparison to a reference standard may be appropriate and applicants should consider the need to perform pharmacokinetic/pharmacodynamic (PK/PD) studies even in cases where the chemical/physical testing shows comparability.

Tests should include those routinely used for release of the active pharmaceutical ingredient, and where appropriate additional tests specifically directed at fully evaluating the impact of the change. A re-evaluation of the in-process controls should be undertaken to ensure that appropriate monitoring is performed at the critical decision making steps and at points where data serve to confirm consistency of the process. A re-assessment of the critical controls - those that must be controlled with predetermined criteria to ensure that the drug substance meets its specification - should also be addressed. For biotechnology-derived products, final drug product testing or additional drug substance stability studies may also be necessary to fully evaluate the impact of the change on the product.

It should be emphasized that the data package that is included in the regulatory submission is only a subset of the entire information required to support the manufacturing chromatography process change. It is expected that the relevant cGMP information (environmental, instrument qualification, etc.) will be executed, appropriately documented, and available for review upon a facilities inspection. For biotechnology-derived products registered in a BLA, some major changes at an existing facility (i.e. those that have a substantial potential to adversely affect the product) may require, under 21 CFR 601.2(d), a satisfactory cGMP compliance status prior to distribution of the product made with the change.

The responsibility for reporting changes of the type described in this guidance lies with the party that owns the application.

Although this document is intended to provide guidance on regulatory reporting categories when implementing changes in chromatographic processes inherently it can not be comprehensive enough to cover all specific cases. Multiple factors should be addressed before the company can decide on a most effective and safe path. Key factors to consider when changing manufacturing chromatography systems are listed in appendix A.

IV. ASSESSMENT OF CHANGE

A holder of an approved application must assess the effects of the change before distributing a drug product made with a manufacturing change (section 506A(b) of the Act, and section 351 of the PHS Act). A central tenet of this guidance is that a given change in the drug substance manufacturing process can be adequately assessed by comparing pre- and post-change materials, and demonstrating that the post-change material is comparable to the pre-change material (i.e. of the same or better quality, as described below). For biologically-derived products, it should be noted that better quality does not always mean "more pure". In certain products the impurities could act as stabilizers, or act to enhance or

inhibit the activity of the active ingredients. For example, a more highly pure product (which can also be the case with less pure product) may cause an immunogenic response or product aggregation.

When comparability cannot be demonstrated solely with chemical and physical testing, applicants should submit a prior approval supplement and should consider appropriate tests for qualification of impurities, assessment of stability and the need to perform PK/PD studies to demonstrate comparability. If physicochemical comparability cannot be demonstrated on the production batch, then the change has a substantial potential to have an adverse effect on the identity, strength, quality, purity, and/or potency of the drug product. An applicant still wishing to institute such a change would be expected to provide additional information in support of the change, such as in-vitro or in-vivo biological studies, or human clinical trials.

The stability of some drug products can be affected by small changes in impurities (e.g., increases in the trace levels of heavy metals). For drug products with a potential for stability problems, the first production batch(es) of drug product made with post-change drug substance should be included in the applicant's stability testing program.

Two major factors for determining comparability in the drug substance are the impurity profile (both product and process related impurities) and physical/structural properties. For the purposes of this guidance, only these factors will be discussed. However, other factors that can be important in individual cases should be evaluated to demonstrate comparability. For example, if the drug substance is defined as a mixture of active analogs, the ratios after the change should be within the stated acceptance criteria, or if not stated, within the upper and lower statistical limits of historical data. For small molecules, the two physical/structural properties of the drug substance, morphic form[1] and particle size, are considered critical for evaluation of comparability, established after the last true solution. In the case of a biological product, materials leading to safety concerns, such as the removal of adventitious agents from the process stream, should also be considered.

Comparability of Impurity Profiles

The impact of manufacturing modifications on the impurity profile is evaluated by determining levels of existing impurities, and new impurities. It is important to determine the stage in the manufacturing process at which impurities should be evaluated, and to establish the adequacy of the analytical procedures used for this purpose. Process impurities may consist of both small and large molecules. Levels of residual solvents and inorganic substances, resin and filter leachables, detergents, and cell culture media components are examples of small molecules, while host cell proteins and DNA are examples of large molecules, which should be considered during evaluation of the impurity profile.

[1] For the purposes of this guidance, morphic forms also includes hydrates, solvates and amorphous materials

Ideally, impurities should be evaluated in the in-process product immediately following the unit operation step in which the manufacturing modification is made. If it can be shown that the impurity profile of an intermediate material following the modified step is comparable (as defined below), the impurity profile of the drug substance will be considered unaffected by the modification. If comparability cannot be demonstrated immediately following the change, the impurity evaluation can be extended to the next downstream unit operation in-process product, and the evaluation process repeated until the drug substance is reached. Comparability can be demonstrated on any single unit operation in-process product or on the drug substance. For biotechnology-derived products, it is likely that in addition to demonstrating comparability at the unit operation that the final drug substance should be tested in order to demonstrate comparability. If testing is performed on the drug substance, comparability should be established for (1) the product related impurity profile; (2) the physical properties, if relevant to the finished dosage form performance; and 3) removal of process related impurities.

The FDA recognizes that it may not always be possible to establish comparability prior to or at the final drug substance. For example, adequate analytical procedures may not be available, cannot be developed, or, in some cases historical data may not exist. When it is not feasible to evaluate the impurities profile at a unit operation in-process product step, or when comparability cannot be demonstrated at these process stages, the testing can be carried out on the final drug product (with the appropriate assessment of the reporting category based on potential to adversely impact the product).

The analytical procedures used to evaluate the change should be adequate for quantitating both existing and new impurities at the recommended levels. Development of new analytical procedures may be called for. When new analytical procedures are developed for this purpose, a summary of validation or verification data should be provided. The same analytical procedure should be used when comparing impurity levels in pre- and post-modification batches.

Product and Process Related Substances

The level of product-related impurities should be assessed through the side-by-side comparison of post-modification batches to the historical data from representative pre-modification batches and/or reference standard samples. For the purpose of this Guidance for Industry, representative pre-modification batches are production scale batches of drug substance that meet all specification acceptance criteria or production scale batches of a unit operation in-process product that has successfully met all forward processing acceptance criteria for previous process steps. The assessment of impurities should normally be carried out soon after manufacture. However, retained samples can be used for the comparison, provided they have been validated to show no trend toward the level of any impurity significantly increasing/decreasing over time.

The impurities profile will be considered comparable after a given change if three consecutive post-modification batches of either an isolated intermediate or the drug substance are evaluated and the test data for each batch demonstrate that 1) no new impurity is observed that exceeds the ICH Q3A identification threshold of 0.1%; 2) that the level of each specified or existing impurity does not exceed current specification limits or statistical historical ranges for the particular impurity; and 3) the level of total impurities does not exceed the current specification limits or statistical historical ranges for the sum of impurities. When comparing pre- and post-modification batches both process related and product related impurities should be evaluated. The appropriateness of implementing a 0.1% limit should be assessed in light of the limit being dependent on dose. Lower thresholds may be appropriate, particularly for biotechnology-derived drug substances, based on scientific rationale and level of concern. For example, a change in any single impurity (such as a toxin) could potentially have a large impact on safety and/or efficacy.

Additional principles regarding comparability of impurity profiles are outlined below.

- The batches of the unit operation in-process product or drug substance used for testing should be manufactured using exclusively the material that has been subjected to the change(s) (i.e., without blending with prechange material).

- Raw materials introduced into the process (e.g. new salts, stationary phases) shall be evaluated for potential impact on the impurity profile and product quality, safety and efficacy.

- Changes can be evaluated using data from qualified smaller scale batches representative of the full scale batches provided the FDA deems appropriate experience exists with the manufacturing process. If comparability is demonstrated by, and the filing based on, smaller scale batches, the first production batch should also be evaluated for comparability.

- Each existing impurity shall remain within its stated limit or, if not stated, within the statistical upper and lower limit range of historical data.

- Total impurities shall remain within the stated limit or, if not stated, at or below the upper statistical limit of historical data (with the understanding that for biotechnology-derived products, below the historical impurities level may impact product quality).

- Comparability of the impurity profile can be established by testing an appropriate isolated intermediate following the change or the final drug substance. For biotechnology-derived products, even if comparability can be demonstrated for an isolated intermediate, it may be necessary to test final drug substance.

- Comparability may be established by combining results from multiple unit operation in-process products collected at different steps downstream of the process change. For example, in a 12 step process, the process impurities may be evaluated at Steps 2 and 8, while product impurities are evaluated at Steps 5 and 9.

- If impurity profile differences, or other changes in the molecule are observed as a result of the chromatography system change, preclinical studies, including safety and PK studies, may be required. The observed impurity profile differences should be discussed with FDA reviewer(s). Furthermore, observed impurity profile differences may require revalidation of subsequent process steps, including viral clearance evaluation and other clearance studies (e.g., DNA, HCP, Protein A). In some cases, clinical studies may be required (e.g. change in glycosylation pattern if glycosylation has been demonstrated to be a key functional attribute).

- In addition, it should be noted that the use of pilot scale data to support changes for specified biotechnology-derived products must be justified. Scaled-down processes used to demonstrate removal of adventitious agents must be based on sound scientific principles to ensure the process is representative of the full-scale commercial process.

In addition, levels of process residuals (solvents and inorganic substances, buffer components, detergents, cell culture media components) and/or other in-process related small molecules should also be considered during evaluation of the impurity profile.

- Each existing in-process reagent is within its stated limit or, if not stated, is within the upper and lower statistical limit range of historical data.

- New residual solvents, in either a unit operation in-process product, or the drug substance, are at or below the levels recommended in the ICH guidance Q3C Impurities: Residual Solvents. A toxicological assessment may be necessary if ICH impurity levels are not met.

- An assessment of the impact of residual solvents levels on the stability of the drug substance.

Comparability of Physical Properties

For specified biotechnology-derived products, the physical properties of the drug substance can be impacted by changes made to the chromatography system. Changes such as column chemistry (mobile and stationary phase) or temperature could potentially modify a biotechnology-derived product. For example, changes to chromatographic resin can affect the levels of product related variants, aggregates and/or glycosylation patterns of the product. Bioassays and/or PK/PD studies may be required for biotechnology-derived products as many physicochemical tests would not

be able to accurately detect small changes in the product. Animal testing may be required as in-vitro bioassays may not show potential changes in the product's tertiary structure.

For small molecule products, in general, the physical properties of the drug substance are not likely to be affected by changes made to the chromatography system. Generally, the only way changes can affect the physical properties of the drug substance is by carryover of new impurities or higher levels of existing impurities into the final drug substance. Although minor differences in the impurity profile at this stage are unlikely to cause physical property modifications to the drug substance, the possibility of such changes in physical properties should be considered. Consequently, physical properties of the drug substance, when they are relevant to finished dosage form performance, should be evaluated unless comparability of the impurity profile can be demonstrated prior to the final solution step (e.g., on the crude drug substance or an earlier unit operation in-process product). Generally, only two physical properties of the drug substance, morphic form[1] and particle size, are considered critical for evaluation of comparability. However, other physical properties may be important in individual cases.

The physical properties of the drug substance will be considered comparable after a given change if post-modification batches of the final drug substance are compared to representative pre-modification batches and the test data for each batch demonstrate:

- Each existing impurity is within its stated limit or, if not stated, is within the upper and lower limits of historical data.

- Total impurities are within the stated limit or, if not stated, are within the upper and lower limits of historical data.

In addition, for small molecules, the physical properties of drug substance will be considered comparable after a given change if at least three post-modification batches of the drug substance are prepared and the data demonstrate:

- Conformance to established acceptance criteria for morphic form or, where acceptance criteria do not exist, the isolation of the same form or mixture of forms within the range of historical data, and

- Conformance to historical particle size distribution profile.

V. TYPES OF CHANGE

Documentation

The manufacturing process changes discussed in this section cover all aspects of the chromatography system. The following documentation requirements apply to all changes:

- Description of the change and rationale for the proposed change and reporting category.

- A summary of any pertinent variation in equipment, raw materials, or operating conditions.

- A description and summary of validation or verification data for any new analytical procedure and also for existing procedures if their use is being extended beyond their original purpose. The additional validation/verification data that should be submitted will depend on the individual case and is to be consistent with ICH Guidance (Q2A and Q2B) on method validation.

- Data to support the evaluation of the impurity profile (both process and product related), physico-chemical properties and changes in product related impurities. Validation or verification data to support that the process will consistently meet in-process acceptance criteria following the change.

- Data to support the evaluation of drug substance and/or drug product stability consistent with ICH Guidance Q1A and Q5C.

- Specifications (tests and acceptance criteria) for new reagents and solvents and Certificates of Analysis from suppliers, if applicable. When a new solvent or other raw material or component is introduced into the process, the possibility of carryover into the drug substance should be assessed. When a new resin is introduced for biotechnology-derived products, potential leachables should be assessed.

- If a move to a new facility, the name and address and other pertinent organizational information for the new facility. For biotechnology-derived products, a list of the products produced in the facility in the same areas and a description of precautions to prevent contamination/cross contamination. If applicable, the date of the last successful FDA inspection of the site for similar type operations.

Change Tables

The following tables provide guidance on the CMC documentation and regulatory reporting categories for a given chromatography system manufacturing change based on the potential to adversely affect the identity, strength, quality, purity or potency of a product as they relate to the safety or effectiveness of the product. Examples of changes within a category are given. The appropriate reporting category can only be determined using a risked-based approach. The proposed regulatory reporting category for a given example is only appropriate if supported by full array of comparability data test documentation.

Although the following tables describe the appropriate test documentation and reporting category for an individual change, it is acknowledged that changes to a chromatographic system often involve various combinations of individual changes. For example, a site change may also involve column equipment and manufacturing process changes or a component and composition change may necessitate a column scale-up change. For multiple related changes where the recommended reporting categories for the individual changes differ, it is recommended that the filing be in accordance with the most restrictive of those recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, it is recommended that the filing be in according with the reporting category for the individual changes. However, an assessment on the potential impact to the product due to the cumulative affect of the multiple changes should be performed to determine if a higher reporting category is warranted (e.g. multiple CBE-30 changes bundled together and with the reporting category bumped up to a Prior Approval Supplement).

Changes are categorized into three levels

- Minimal changes are those that FDA has identified as having a minimal potential to adversely affect the identity, strength, quality, purity, or potency of a product as they relate to the safety or effectiveness of the product. These changes are reported in an Annual Report.

- Moderate changes are those that FDA has identified as having a moderate potential to adversely affect the identity, strength, quality, purity, or potency of a product as they relate to the safety or effectiveness of the product. These changes are reported either as CBE or CBE-30 Supplements.

- Substantial changes are those that FDA has identified as having a substantial potential to adversely affect the identity, strength, quality, purity, or potency of a product as they relate to the safety or effectiveness of the product. These changes are reported as Prior Approval Supplements.

534 **1. MOBILE PHASE**

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536 This section of the guidance focuses on changes in the concentration of reagents or a change in the components and/or composition of
537 reagents used in the mobile phase.

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539 A. Small Molecules

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Change	Examples	Test Documentation	Reporting Category
Minimal Potential	Change in the buffer concentration (e.g. 0.1M to 0.2M phosphate buffer).	Application/compendial release requirements. Additional data to support the change as appropriate.	Annual Report
Moderate Potential	Change in the elution buffer pH. Change in the slope for a gradient system (e.g. 40 minutes to 30 minutes to reach 50% Buffer B) that alters the peak elution times. Change in the type of salt used (e.g. ammonium chloride to sodium phosphate). Change in organic constituent of the mobile phase (e.g. acetonitrile to methanol).	Application/compendial release requirements. Specifications for new reagents or solvents, if applicable. Data on up to three consecutive batches made using the new mobile phase, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.	Before and including the final intermediate step: Annual Report After the final intermediate step: CBE-0 Supplement.
Substantial Potential	None Identified		

541 B. Specified Biotechnology-Derived Products

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	Change in solvent or salt manufacturer. Change in the pH or salt concentration for a wash or regeneration step.	Application/compendial release requirements. Additional data to support the change as appropriate. Assessment of no impact on column lifetimes, carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current removal factor is decreased by change.	Annual Report
Moderate Potential	Change in the elution buffer concentration (e.g. 0.1 M to 0.2M phosphate buffer). Change in the elution buffer pH. Change in the type of salt used (e.g. sodium chloride to sodium acetate). Change in the elution condition (e.g. slope for a gradient system) that alters the peak elution times. Changes in organic constituent of the mobile phase (e.g. acetonitrile to methanol).	Application/compendial release requirements. Assessment of no impact on column lifetimes, carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current removal factor is decreased by change (based on nature or source of new salt or solvent). Data on up to three consecutive batches made using the new mobile phase, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance. Stability Testing: Significant body of information available: One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report. Significant body of information not available: Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report.	CBE-0/CBE-30 Supplement. Long term stability data reported in AR
Substantial Potential	None Identified		

542 **2. STATIONARY PHASE**

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544 This section of the guidance focuses on changes in the components and composition of the stationary phase.

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546 A. Small Molecules

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Change	Examples	Test documentation	Reporting Category
Minimal Potential	Change in solid support parameters (e.g. pore size, particle size, etc.).	Application/compendial release requirements. Additional data to support the change as appropriate (e.g. vendor's support files).	Annual Report
Moderate Potential	Change in composition of the solid support (silica to polymer based). Change in the ligand spacer arm of the bonded phase but keeping the same basic separation mode (e.g. C18 to C8 on a silica support). Change in the chemical nature of the bound ligand (e.g. cyano to an octadecyl resin).	Application/compendial release requirements. Data on up to three consecutive batches made using the new stationary phase, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance. Additional data to support the change as appropriate (i.e. evaluation on potential leaches)	Before and including the final intermediate step: Annual Report After the final intermediate step: CBE-0 Supplement.
Substantial Potential	None Identified		

548 B. Specified Biotechnology-Derived Products

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	Change in solid support parameters (e.g. pore size, particle size, etc.) that does not affect mode of separation.	Application/compendial release requirements Additional data to support the change as appropriate. Assessment of no impact on column lifetimes, carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current removal factor is decreased by change.	Annual Report
Moderate Potential	Change in the method of manufacture of the ligand. No change in the ligand or coupling chemistry (e.g. manufacture change to remove animal sourced materials for an affinity resin). Change in the manufacturer of the packing material. Change in composition of the solid support (e.g. silica to polymer based). Change in the chemical nature of the bound ligand (e.g. cyano to octadecyl resin).	Application/compendial release requirements. Evaluation of leachables, capacity and yield. Additional data to support the change as appropriate (e.g. vendor's support files). Prospective or concurrent resin lifetime studies to level of previously used resin. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change (based on nature or source of new solid support or ligand). Data on up to three consecutive batches made using the new stationary phase, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance. Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report. <u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report.	CBE-0/CBE-30 Supplement. Long-term stability data reported in AR.
Substantial Potential	None Identified		

549 **3. CHROMATOGRAPHIC CONDITIONS**

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551 This section of the guidance focuses on changes in the components and parameters in chromatographic conditions (e.g. temperature,
552 pH, reagent stoichiometry, time, collection criteria, and column lifetime).

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554 A. Small Molecules

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Change	Examples	Test Documentation	Reporting Category
Minimal Potential	Changes in column cleaning and/or regeneration (e.g. additional washing or equilibration step, change in regeneration buffer composition). Changes in column storage conditions (e.g. storage at pH 4 instead of pH 7) within resin manufacturer's stability specifications. Changes in column operational temperature. Changes in linear mobile phase flow rate (e.g. from 50 cm/hr to 100 cm/hr) in other phases than the elution phase. Extended column lifetime supported by body of historic data including evaluation of impurity profile, carry-over, physical characteristics (e.g. back pressure).	Application/compendial release requirements. Additional data to support the change as appropriate (e.g. impact of storage conditions on resin lifetimes).	Annual Report
Moderate Potential	Increase in column loading (e.g. from 8 gm/ L of resin by reversed-phase HPLC to 12 gm/ L). Changes in linear mobile phase flow rate (e.g. from 50 cm/hr to 100 cm/hr) in the elution phase. Changes in load composition (e.g. pH, conductivity, solvent composition and product	Application/compendial release requirements. Data on up to three consecutive batches made using the new chromatographic conditions, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.	Before and including the final intermediate step: Annual Report After the final intermediate step: CBE-0 Supplement.

	concentration). Changes in collection criteria resulting in a higher pool volume or shift in collection window. Changes in holding time or temperature for intermediates. Changes of in-process program (e.g. deletion of a process control or an analytical method).		
Substantial Potential	None Identified		

556 B. Specified Biotechnology-Derived Products

557

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	Changes in column cleaning and/or regeneration (e.g. additional washing or equilibration step, change in regeneration buffer composition) with assessment of no impact on carry-over of impurities and viral clearance. Changes in column storage conditions (e.g. storage at pH 4 instead of pH 7) within resin manufacturer's stability specifications. Extended column lifetime supported by body of historic data including evaluation of impurity profile, carry-over, physical characteristics (e.g. back pressure).	Application/compendial release requirements. Additional data to support the change as appropriate (e.g. impact of storage conditions or regeneration buffer on resin lifetime). Assessment of no impact on column lifetime, carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change.	Annual Report
Moderate Potential	Changes in flow rate (e.g. from 50 cm/hr to 100 cm/hr) for the elution, cleaning and/or regeneration phase with assessment of no impact on carry-over of impurities and viral clearance. Changes in column operational temperature. Changes in load composition (e.g. pH, conductivity and product concentration). Changes in collection criteria resulting in a higher pool volume or shift in collection window. Increase in column loading (e.g. from 8 gm/L of resin by reversed-phase HPLC to 12 gm/L).	Application/compendial release requirements. Revalidation of lifetimes of resin might be required to demonstrate that the increased load does not adversely impact the ability of the resin to clear impurities over its lifetime. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change (based on source and raw materials). Data on up to three consecutive batches made using the new chromatographic conditions, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of	CBE-0/CBE-30 Supplement. Long-term stability data reported in AR.

	Changes in holding time or temperature for intermediates. Changes of in-process program (e.g. deletion of a process control or an analytical method).	change on drug substance. Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR. <u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR.	
Substantial Potential	None Identified		

558 **4. EQUIPMENT**
559
560 This section of the guidance focuses on changes in the chromatography system, both in design and composition.
561
562 A. Small Molecules
563
564 A change to new equipment that is not significantly different from that previously used, with no modifications to process parameters,
565 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out. However,
566 installation qualification and operational qualification information should be retained in-house and is subject to FDA's review at its
567 discretion.
568

Change	Examples	Test documentation	Reporting Category
Minimal Potential	None Identified		
Moderate Potential	After the final intermediate step: New equipment is significantly different from that previously used (e.g. switching from glass to metal columns).	Application/compendial release requirements. Data on up to three consecutive batches made using the new equipment, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance.	CBE-0 Supplement. .
Substantial Potential	None Identified		

569 B. Specified Biotechnology-Derived Products
570

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	Change or addition of alternative equipment of the same scale, design and operating principles. ("like-for-like" change, all wetted materials as currently specified in application) listed as major equipment in the registration. Change in wetted component material (e.g. from fixed stainless steel tanks to plastic bags for buffers, from stainless steel to polymer frits, from different elastomer for seals or glass to stainless steel column (all wetted materials characterized/currently used in process). Modification of chromatography equipment intended only to improve column/packing performance (improvements of flow distributors or change from standard column to pack-in-place column with no new materials of construction).	Application/compendial release requirements. Additional data to support the change as appropriate (e.g. moving from glass to stainless steel an assessment of corrosion using high salt concentration; evaluation of potential leaches).	Annual Report

Moderate Potential	Replacement of column equipment with that of similar, but not identical, design and operating principle. Change from non-automated or non-mechanical equipment to automated or mechanical equipment.	Application/compendial release requirements. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Data on up to three consecutive batches made using the new equipment, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. Revalidation of process step may be considered. One batch on long-term stability, data reported in AR.	CBE-0/CBE-30 Supplement. Long-term stability reported in AR
Substantial Potential	Replacement of column equipment which operate with a different operating principle (e.g. packed bed to expanded bed).	Application/compendial release requirements. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Data on up to three consecutive batches made using the new equipment, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR. <u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR.	Prior Approval Supplement Long-term stability reported in AR

5. CHANGES IN COLUMN SIZE (Scale-up/Scale-down)

This section of the guidance focuses on changes to the size of columns used in the manufacturing process. Post-approval changes in the size of the column to larger or smaller production columns call for submission of additional information in the application.

A. Small Molecules

Many scale changes need not be filed with the Agency, and equivalence testing as described in this document need not be carried out. However, installation qualification and operational qualification information should be retained in-house and is subject to FDA's review at its discretion.

Change	Examples	Test documentation	Reporting Category
Minimal Potential	Before the final intermediate step: Change in column size (e.g. an increase in column diameter from 45 cm to 60 cm). Equipment of a different capacity may be used in conjunction with these changes.	Application/compendial release requirements. Additional data to support the change as appropriate.	Annual Report
Moderate Potential	After the final intermediate step: Change in column size (e.g. an increase in column diameter from 45 to 60 cm). Equipment of a different capacity may be used in conjunction with these changes.	Application/compendial release requirements. Data on up to three consecutive batches made using the new column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.	CBE-0 Supplement.
Substantial Potential	None Identified		

582 B. Specified Biotechnology-Derived Products

583

Change	Examples	Testing Documentation	Reporting Category
Minimal Potential	None Identified		
Moderate Potential	Increased/decreased column diameter (fold increase not important) maintaining same bed height. Assuming proportional load and wash volumes remain constant, also pooling parameters remaining constant.	Application/compendial release requirements. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Assessment of the need to perform/not perform revalidation of the process step. Data on up to three consecutive batches made using the new column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. One batch on long-term stability, data reported in AR.	CBE-0/CBE-30 Supplement. Long-term stability data reported in AR.

Substantial Potential	Increased/decreased column size – changing bed height and column diameter and/or making changes to the load or washes to the column.	Application/compendial release requirements. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Revalidation of the column lifetimes and process required as the proportions of load and washes are changing, or the bed height is different. Data on up to three consecutive batches made using the new column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR. <u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in AR.	Prior Approval Supplement. Long-term stability data reported in AR.

584 **6. ADDITION/SUBTRACTION OF COLUMN(S)**
585
586 This section of the guidance focuses on changes in the number of columns used at a particular process step, and on the addition,
587 substitution or elimination of a chromatography step. These changes call for submission of additional information in the application.
588
589 A. Small Molecules
590

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	None Identified		
Moderate Potential	Change in the manufacturing process to 1) remove an existing chromatography step, 2) add an additional chromatography step or 3) substitute an existing non-chromatography step with a new chromatography step.	Application/compendial release requirements. Data on up to three consecutive batches made using the new column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance.	Before the final intermediate step: Annual Report At the final intermediate step: CBE-0 Supplement. After the final intermediate step: CBE-30 Supplement.
Substantial Potential	None Identified		

591 B. Specified Biotechnology-Derived Products

592

Change	Examples	Test documentation	Reporting Category
Minimal Potential	None Identified		
Moderate Potential	Addition or reduction in number of purification columns used for a unit operation to achieve a change in purification scale not associated with a process change.	Application/compendial release requirements. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Data on up to three consecutive batches made with addition or subtraction of the column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. One batch on long term stability, data reported in AR.	CBE-30 Supplement. Long-term stability data reported in AR.

Substantial Potential	Change in the manufacturing process to 1) remove an existing chromatography step, 2) add an additional chromatography step or 3) substitute an existing non-chromatography step with a new chromatography step.	Application/compendial release requirements. Assessment of the need to perform/not perform revalidation of the process step and subsequent downstream steps to demonstrate no impact on product. Assessment of no impact on carry-over of impurities or impact on viral clearance. Revalidation of virus or adventitious agent removal or inactivation if current studies are invalidated by change. Data on three consecutive batches made using with either the addition or subtraction the column(s), historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. Stability testing: <u>Significant body of information available</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in Annual Report <u>Significant body of information not available.</u> Three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in Annual Report.	Prior Approval Supplement. Long-term stability data reported in AR.

593

7. SITE CHANGES

Site changes include changes in location of the site of manufacture of intermediates and the drug substance for both company-owned and contract manufacturing facilities. Site changes can involve the addition of new facilities or the relocation of manufacturing facilities approved in the referenced application(s). The term "No changes in equipment" is meant to encompass both the same equipment being moved from one facility to another or new equivalent equipment being purchased and placed in a new facility. Transfer of an existing manufacturing step to a facility approved for other manufacturing steps should be considered a site change. Equipment changes (Section IV.4.) may often accompany a site change and should be considered under multiple related changes (Section IV.8.) with the filing moving to the most restrictive of those individual changes. Cross contamination should be considered when the site change results in the product moving into a facility already manufacturing product, with an awareness of the increased potential for adverse impact when moving from a single to a multi-product facilities. Any changes in the site of manufacture that are not prior approval supplements can only fit this category if a recent (last 2 years) acceptable cGMP inspection for the type of operation involved has occurred. Any site change requiring a pre-approval inspection will need to be reported as a PAS with the exception of small molecule drug substance intermediates.

A. Small Molecules

Site changes within a single facility need not be filed with the Agency, and equivalence testing as described in this document need not be carried out. However, installation qualification and operational qualification information should be retained in-house and is subject to FDA's review at its discretion.

Change	Examples	Test documentation	Reporting Category
Minimal Potential	A move of a chromatographic step to a different manufacturing site for drug substance intermediates, prior to the final intermediate.	Application/compendial release requirements. Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. Certificate of Analysis from the manufacturer for each outsourced intermediate affected by the site change.	Annual Report

Moderate Potential	A move to a different manufacturing site within the same company outside of the current manufacturing campus (different central file number). A move to a new site owned by a contract manufacturer not previously approved for the chromatography step(s) being transferred. A restart at the previous manufacturing site for the type of operation that has been discontinued for at least two years.	Application/compendial release requirements. Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. The new site should have similar environmental controls (e.g., temperature, humidity, cross contamination). Data on at least three consecutive batches made at the new site, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. Certificate of Analysis from the manufacturer for each outsourced intermediate affected by the site change.	Prior to and including the final intermediate step: CBE-0 Supplement After the final intermediate step: CBE-30 Supplement
Substantial Potential	A move to a different manufacturing site when the site does not have a satisfactory cGMP inspection for the type of operation that is being moved. Does not apply to intermediates.	Application/compendial release requirements Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. The new site should have similar environmental controls (e.g., temperature, humidity, cross contamination). Data on at least three consecutive batches made at the new site, historical data for comparison, and a description of the source of the historical data. Additional characterization data as needed to show comparability and supportive historical development studies to demonstrate no adverse impact of change on drug substance. Certificate of Analysis from the manufacturer for each outsourced intermediate affected by the site change.	Prior Approval Supplement.

615 B. Specified Biotechnology-Derived Products
616

Change	Examples	Test Documentation	Reporting Category
Minimal Potential	A move of a chromatography system from the first floor of a building to the second floor of the building. A move of a chromatography system from one building to another building within the same campus with no changes to the equipment, or other operating parameters (i.e. same skids etc).	Application/compedial release requirements. Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. List of other products made in the area if multi-product facility addressing the potential for contamination/cross contamination or exposure to other processes that could change the status of the adventitious agent concerns.	Annual Report
Moderate Potential	A move to a different manufacturing site within the same company outside of the current manufacturing campus (different central file number) with assessment of no impact on viral clearance. A move to a new site owned by a contract manufacturer not previously approved for the chromatography step(s) being transferred. A restart at the previous manufacturing site for the type of operation that has been discontinued for at least two years.	Application/compendial release requirements. Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. List of products produced in the facility in the same areas if a multi-product facility and description of precautions to prevent contamination /cross contamination. Identical but new equipment, and identical operating and process parameters should apply. The new site should have similar type of environmental controls (e.g., temperature, humidity, cross contamination). Data on up to three consecutive batches made at the new site, historical data for comparison and a description of the source of any historical data. Additional characterization data as needed to show comparability and appropriate supportive historical development studies to demonstrate no adverse impact of change on drug substance. Stability Testing: Up to three months of stability data on the first batch, and a commitment to three batches of DS on long-term stability, and one batch of DP made from the DS.	CBE 30 Supplement. Long-term stability data reported in AR.

Substantial Potential	A move to a different manufacturing site when the new manufacturing site does not have a satisfactory cGMP inspection for the type of operation that is being moved.	Application/compendial release requirements. Concise description of the manufacturing steps being transferred, a summary (with justification) of any pertinent variation in equipment or process. List of products produced in the facility in the same areas if a multi-product facility, simple floor plan, description of precautions to prevent contamination/cross contamination. The new site should have similar type of environmental controls (e.g., temperature, humidity, cross contamination). If contract manufacturer, reference to a written agreement for contract manufacturer and responsibilities of each party. Data on up to three consecutive batches made at the new site, and comparison of the DS from the new site to previously manufactured DS, with additional characterization data as needed to show comparability, and a description of the source of the historical data. Stability Testing: <u>Significant body of information available:</u> One batch with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report. <u>Significant body of information not available:</u> Up to three batches with three months accelerated stability data reported in supplement; one batch on long-term stability, data reported in annual report.	Prior Approval Supplement. Long-term stability data reported in AR.

8. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve column equipment and manufacturing process changes or a component and composition change may necessitate a column scale-up change. For multiple related changes where the recommended reporting categories for the individual changes differ, it is recommended that the filing be in accordance with the most restrictive of those recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, it is recommended that the filing be in according with the reporting category for the individual changes, with an assessment of the impact of the multiple changes. The cumulative effect of multiple changes should be determined not to increase the risk of an adverse effect on the product.

VI. REFERENCES

A. Code of Federal Regulations 210.3(b)(2) and (10), 310.3(b) and (g), and 320.1(a) and (e).

B. "Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Substances," U.S. Department of Health and Human Services, Food and Drug Administration, February 1987.

C. "Guideline for Industry: Stability Testing of New Drug Substances and Products" U.S. Department of Health and Human Services, Food and Drug Administration, September 1994.

D. "Guidance for Industry: Immediate Release Solid Dosage Forms; Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation", November 1995)

E. "FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products", U.S. Department of Health and Human Services, Food and Drug Administration, April 1996

F. "Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls Information for Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for In Vivo Use", U.S. Department of Health and Human Services, Food and Drug Administration, August 1996.

G. "Guidance for Industry – Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products", U.S. Department of Health and Human Services, Food and Drug Administration, July 1997.

H. "Guidance for Industry – Changes to an Approved NDA or ANDA", U.S. Department of Health and Human Services, Food and Drug Administration, November 1999.

I. "Guidance for Industry – BACPAC I: Intermediates in Drug Substance Synthesis", U.S. Department of Health and Human Services, Food and Drug Administration, February 2001.

J. "Guidance for Industry – Comparability Protocols – Chemistry, Manufacturing and Controls Information" Draft Guidance. U.S. Department of Health and Human Services, Food and Drug Administration, February 2003.

K. "Guidance for Industry – Comparability Protocols – Protein Drug Products and Biological Products - Chemistry, Manufacturing and Controls Information" Draft Guidance. U.S. Department of Health and Human Services, Food and Drug Administration, September 2003.

L. ICH Q1A. Stability Testing of New Drugs and Products

M. ICH Q6A. Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

N. ICH Q6B. Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

O. ICH Q7A. Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

APPENDIX A

Factors to Consider When Changing Chromatographic Systems

1. What is the modality of the separation (e.g. reversed-phase, size –exclusion, ion-exchange, etc.)?
2. What does the separation accomplish in the process (e.g., removal of product variants, reactants, host proteins, process residuals, adventitious agents, etc.)?
3. What is the mechanism of action and how will this be impacted by the change?
4. Can the available assays adequately assess the impact of the change on the intermediate or drug substance? With statistical significance?
5. Will the change impact any downstream step? If so, include this in the assessment.
6. Are the tools to assess comparability up to the job (i.e., matched to the complexity of the drug substance)?
7. Will the change impact the stability of the intermediate, drug substance or drug product or the validity of the reported stability studies?
8. How will the change impact the robustness or/and the reproducibility of the process?
9. Does the quality and quantity of the data support the assessment of how the change can affect the quality and properties of intermediate products, drug substance or drug product?
10. Does a risk – benefit analysis support making the change?
11. What is the impact on microbial control in the process (e.g. bacterial/fungal growth and the capability of the process on endotoxin removal)? What is the impact of the change on validation of removal of specific impurities such as endotoxin?
12. Is the change within or outside the range of previously reported data (e.g. a parameter changed from one value to another value should be compared to the validated range)?
13. What affect will the change have on the validity of previous virus or adventitious agent removal or inactivation validation studies?
14. What effect will the change have on the processing times? Will the time increase? What is the impact of this on the risk of an adverse effect?
15. What effect will the change have on potential for contamination or cross contamination of the product?
16. What are the immunogenic consequences of the change (based on structural analysis and content of di- and polymeric aggregates)?

APPENDIX B

Active Pharmaceutical Ingredient Characterization Tests

Information from specific tests regarding identity, purity, stability and consistency of manufacture of the drug substance should be provided.

Examples of analyses for which information may be submitted for specified biotechnology-derived products include, but are not necessarily limited to the following:

- Amino acid analysis
- Amino acid sequencing, entire sequence or amino-and carboxy-terminal sequences
- Peptide mapping
- Determination of disulfide linkage
- Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE)
- Isoelectric focusing
- Conventional and high-pressure liquid chromatography (HPLC) e.g. reversed-phase, size exclusion, ion-exchange, etc.
- Mass spectrometry
- Carbohydrate Analysis
- Assays to detect product related proteins including deamidated, oxidized, cleaved, and aggregated forms and other variants e.g., amino acid substitutions, adducts/derivatives.
- Assays to detect residual host proteins, DNA, reagents
- Immunochemical analyses
- Assays to quantitate bioburden and endotoxin

Examples of analyses for which information may be submitted for small molecules include, but are not necessarily limited to the following:

- High Performance Liquid Chromatography (reversed phase, chiral)
- Gas Chromatography
- X-Ray
- Laser diffraction (particle size analysis)

APPENDIX C: GLOSSARY

Acceptance Criteria: Numerical limits, ranges, or other criteria for the test described.

Assess the Effects of the Change: To evaluate the effects of a manufacturing change on the identity, strength, quality, purity, and potency of a drug product as those factors may relate to the safety or effectiveness of the drug product.

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

Biological Tests: Biological tests include animal, cell culture or biochemical based testing that measures a biological, biochemical or physiological response.

Critical: Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the drug substance meets its specification.

Comparability: The quality or state of being suitable for comparison. FDA may determine that two products are comparable if the results of the comparability testing demonstrate that a manufacturing change does not affect identity, strength, quality, purity or potency as they may relate to the safety or effectiveness of the product.

Comparability Protocol: A protocol submitted by an applicant under CFR 601.12(e) and 314.70 (g)(4) that describes the specific tests and validation studies and acceptable limits to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes on the identity, strength, quality, purity and potency of the product as they may relate to the safety or effectiveness of the product. Any such protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution of the product which, if approved, may justify a reduced reporting category for the particular change because the use of the protocol for that type of change reduces the potential risk of an adverse effect.

Contiguous Campus: Continuous or unbroken site or a set of buildings in adjacent city blocks.

Drug Product: A finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)).

Drug Substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Equipment: Automated or non-automated, mechanical or non-mechanical equipment used to produce the drug product, including equipment used to package the drug product.

Equivalence: See comparability

Facility: A physical building with a defined building number or name.

Formulation: A listing of the ingredients and composition of the dosage form.

Historical Data: For purposes of this guidance, data on impurities or physical attributes from three or more consecutive representative premodification batches. The upper statistical limit of an impurity should be based on the mean plus three times the standard deviation. A lower statistical limit can be similarly defined, where appropriate (e.g., the level of an active component, moisture content).

Impurity: Any component of the drug substance that is not the chemical entity defined as the drug substance or an excipient in the drug product (ICH Q6A).

Impurity profile: A description of the identified and unidentified impurities present in a drug substance (ICH A3A).

In-process Material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product (21 CFR 210.3(b)(9))

Intermediate Material: The chemical mixture that may or may not have completed the chemistry steps, and thus is not it its final chemical and physical/conformational state, and has not been through final process steps to final drug substance. Examples in the small molecule world include isolated intermediates, intermediates and final intermediates. Examples in the large molecule world include **Crude Protein Mixtures** (pre transformation, conversion or folding) and purified protein prior to any final polishing steps.

Isolated Intermediate: An intermediate that is obtained as the product after workup of a purification step in the process scheme for the drug substance. The isolation or purification procedure should be part of the validated process. An aliquot of a product that is worked up and/or purified for purposes of characterization does not constitute an isolated intermediate.

Justification: Reports containing scientific data and expert professional judgment to substantiate decisions.

Operating Principle: Rules or concepts governing the operation of the system.

Pilot Scale: The manufacture of a drug substance by a procedure fully representative of and simulating that to be applied to a production scale batch.

Process: A series of operations and/or actions used to produce a desired result.

Range: The extent to which or the limits between which acceptable variation exists.

Same: Agreeing in kind, amount; unchanged in character or condition.

Scale-up: The process of increasing the column volume.

Scale-down: The process of decreasing the column volume.

Similar: Having a general likeness.

Significant body of information: A significant body of information on the stability of the drug product is likely to exist after five years of commercial experience for new molecular entities, or three years of commercial experience for new dosage forms. (Immediate Release Solid Oral Dosage SUPAC; Nov 1995)

Specification: The quality standard (i.e. tests, analytical procedures, and acceptance criteria) provided in the approved application to confirm the quality of API, drug products, intermediates, raw materials, reagents, components, in-process material, container closure systems, and other materials used in the production of the drug substance or drug product.

Total Impurities: The sum of all impurities observed.

Validation: Establishing through documented evidence a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality attributes. A validated manufacturing process is one that has been proven to do what it purports or is represented to do. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, buildings, and personnel), but it also includes the control of the entire processes for repeated batches or runs.

PDA Annual Report Procedures

The PDA Annual Report is one of the most important documents prepared by staff for the membership. Proper *time* and *care* must be given to the preparation, writing, editing, review and approval of this document.

The goal is to publish and deliver to the membership the Annual Report by the end of March of the following year, i.e., March 31, 2005 for the 2004 Annual Report.

Each year, the PDA Annual Report is divided into 12 basic sections: Chair's Message, President's Message, Board of Directors, Science and Technology, Regulatory Affairs and Quality, PDA Training and Research Institute, Programs and Meetings, Membership and Chapters, Financial Report, PDA Awards, and listing of the next year's Board of Directors and PDA Staff.

Each PDA department is responsible for the content—including the accuracy and completeness—of all information in the corresponding section of the Annual Report.

Here is a summary of the procedures and expectations for the creation of this document. Each item in the following outline is explained below:

1. Name an individual in your department to compile information.

2. Information pertaining to members must be accurate and complete.

3. Rosters of volunteer members associated with your department should be available by the end of October. Revisions can be made (see below).

4. Draft of Department's accomplishments should be completed by December 1.

5. Complete Annual Report Verification Sign-Off Form for each version/draft of your material.

Explanation:

1. It is advised that each department name an individual who will be in charge of compiling information for the Annual Report, including the accomplishments of the department, all rosters pertaining to their department (i.e., SAB for the Science and Technology Department, RAQC for Regulatory Affairs and Quality, Chapter Leaders for Membership and Chapters, TRI Faculty, TRI Contributors).

2. It is crucial that all information pertaining to members, i.e., committee rosters, chapter leaders, board of directors rosters, etc., be 100% accurate, complete and consistent from roster to roster. From time to time, a PDA department may contribute information or be asked to review information pertaining to a different section of the document, i.e., the President's Message and the Chair's Message.

3. Rosters should be completed and verified for completeness and accuracy by the end of October. A roster should include the names of all individuals who served on a committee, as faculty/contributor, or as a group/chapter leader during the year. Any changes to the roster in November and/or December should be forwarded to the Marketing Services department immediately via e-mail, with the subject line: "Annual Report, revision to [roster name here]". Before additions or deletions are made to the original

roster, the department head will have to verify the change (see below). Additional instructions will be supplied on how rosters should be formatted, including how to list company names.

4. Each department head will draft the initial review of their department's accomplishments for the year. The write-up should focus as much as possible on accomplishments of members, as well as the accomplishments of the PDA department. The draft should be completed by December 1 of the year for which the Annual Report is being prepared.

5. All PDA department heads will be required to sign the Annual Report Verification Sign-Off Form before the Annual Report can be prepared for final senior-staff review. The department head may be required to sign this form several times, depending on how many changes are made to their documents.

6. After all the sections of the Annual Report are submitted, verified, edited and re-verified, it will be placed into the final format. At this point, **PDA senior staff will be asked to review the document under normal PDA review/approval procedures.** Finally, the Board of Directors will be required to sign-off on the Annual Report before it is finalized and printed.

Annual Report Verification Sign-Off Form

(To be filled out by Marketing Services)

Department:_____

Department Head:_____

Document Under Review:_____

Author of Document:_____

In order for information from any department to be included in the final Annual Report, the department head must review the information and return this form. The department head must verify with their signature that they have read the document, that their department generated the document, that they or someone in their department reviewed the document for completeness and accuracy, and that there are no errors or omissions in the document.

(To be filled out by Department Head)

I verify that I have read and reviewed the _____

for the _____ **Annual Report.**

Signature:_____

Date:_____

I verify that my department generated the document.

Signature:_____

Date:_____

I verify that I and/or my staff have checked to make sure that the information in the document is complete and accurate.

Signature:_____

Date:_____

I verify that I and/or my staff have ensured that there are no errors or omissions in the information provided in the document.

Signature:_____

Date:_____