Chemistry, Manufacturing, and Controls Changes to an Approved Application: Certain Biological Products

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Draft Guidance for Industry

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For questions on the content of this guidance, contact Center for Biologics Evaluation and Research's Office of Communication, Outreach, and Development, 240-402-8010 or 800-835-4709; or for Center for Drug Evaluation and Research, contact Laurie Graham at 301-796-5216.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
December 2017

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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance is intended to assist applicants and manufacturers of certain licensed biological products in determining which reporting category is appropriate for a change in chemistry, manufacturing, and controls (CMC) information to an approved biologics license application (BLA) as specified in 21 CFR 601.12 (i.e., post-approval changes) (Refs. 1 and 2). We (FDA or Agency) describe in this guidance general and administrative information on reporting and evaluating changes and recommendations for reporting categories based on a tiered-reporting system for specific changes under 21 CFR 601.12. This guidance, when finalized, will supersede the guidance entitled "Guidance for Industry: Changes to an Approved Application: Biological Products" dated July 1997 (July 1997 guidance).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 the FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Applicants and manufacturers ("applicants"), for a variety of reasons, often implement changes in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in an approved application for licensed biological products (for purposes of this document, "manufacturing changes"). An applicant must notify the Agency about each change to an approved BLA under 21 CFR 601.12. If the applicant makes a change to an approved BLA, the applicant must also conform to other applicable laws and regulations, including the current good manufacturing practice (CGMP) requirements of section 501 of the

Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(a)(2)(B)) and the regulations in 21 CFR Parts 210, 211, as well as the applicable requirements in 600 through 680 and 820. In addition, section 506A of the FD&C Act (21 U.S.C. 356a) provides requirements for making and reporting manufacturing changes to an approved BLA and for distributing a licensed product made with such a change. Prior to distribution of the product made with a change, an applicant must assess the effects of the change and demonstrate through appropriate validation and/or other clinical and/or non-clinical laboratory studies the lack of an adverse effect of the change on the identity, strength, quality, purity, or potency of the product (for purposes of this guidance, "product quality") as they may relate to safety or effectiveness of the product.[1] In accordance with 21 CFR Parts 210, 211, 600 through 680, and 820, manufacturers must comply with the CGMPs and other applicable requirements and with recordkeeping requirements to ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection.

The FDA issued the July 1997 guidance to assist applicants in determining which reporting mechanism is appropriate for reporting a change to an approved application to reduce the burden on applicants when reporting changes and to facilitate the approval process of the change being made. The FDA is updating the July 1997 guidance to accommodate advances in manufacturing and testing technology and to clarify the FDA's current thinking on assessing reportable changes.

On August 21, 2002, FDA launched the initiative, *Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century - A Risk-Based Approach*[2] (FDA initiative) to stay abreast with new technological advances and enable the Agency to regulate pharmaceutical manufacturing and allocate regulatory resources more effectively. As part of this FDA initiative, the Agency determined that to provide the most effective public health protection, the CMC regulatory review should be based on an understanding of product risk and how best to manage this risk.

We have conducted a review and evaluation of manufacturing changes reported across licensed biological products that are within the scope of this guidance. To determine the appropriate reporting category based on a tiered-reporting system for a specific change, we applied principles of quality risk assessment and risk management consistent with the FDA initiative and the general principles outlined in the Guidance for Industry: Q9 Quality Risk Management (Ref. 3). Based on this evaluation and our overall experience from inspections and review of manufacturing changes, we have revised the recommendations for reporting categories by reclassifying the risks associated with specific changes. Moreover, we have provided additional examples of manufacturing changes to provide further guidance to applicants and manufacturers and assist with making more informed decisions when reporting and implementing post-approval changes. In some instances, these updated recommendations will result in a less burdensome approach for reporting changes, thereby accelerating distribution of the product made with the

[1] 21 CFR 601.12(a)(2).

[2] The final report on the FDA initiative can be found at https://www.fda.gov/downloads/drugs/developmentapprovalprocess/manufacturing/questionsandanswersoncurrentgoodmanufacturingpracticescgmpfordrugs/ucm176374.pdf.

change. These updated recommendations are expected to promote continual improvement and innovation over the product lifecycle and minimize the risks for product shortages. These revisions are consistent with the risk-based regulatory review approach applied by the FDA to the regulation of biological product manufacturing.

III. SCOPE

This guidance applies to certain biological products licensed under the Public Health Service Act (PHS Act).[3] This guidance applies to all manufacturing locations, including contract locations. Licensed biological products that are within the scope of this guidance include:

- Vaccines
- Allergenic products
- Plasma-derived products (e.g., albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors, etc.)
- Antitoxins, antivenins, and venoms
- Naturally-derived protein products (e.g., enzymes, toxins, etc.)
- Cellular, gene and cell-based gene therapy products
- In vitro diagnostics (IVDs) regulated under the PHS Act (e.g., blood donor screening assays, etc.)
- Other biological products licensed under the PHS Act subject to exceptions listed below

This guidance also applies to combination products licensed under a BLA, unless the biological product constituent part is a specified biological product described in 21 CFR 601.2(a).

Biological products that are not within the scope of this guidance include:

- Whole Blood, blood components, Source Plasma, and Source Leukocytes (Ref. 4)
- Specified biological products described in 21 CFR 601.2(a)[4]
- Biosimilar products subject to licensure under section 351(k) of the PHS Act (42 U.S.C. 262(k))

[3] On March 23, 2020, an approved application for a biological product under section 505 of the FD&C Act shall be deemed to be a license for the biological product under section 351 of the PHS Act (see section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009). At that time, this guidance will also apply to changes in CMC information for biological products (such as naturally-derived protein products) whose approved applications under section 505 of the FD&C Act is deemed to be a license under section 351(a) of the PHS Act.

[4] The specified categories of biological products described in 21 CFR 601.2(a) are: therapeutic DNA plasmid products; therapeutic synthetic peptide products of 40 or fewer amino acids; monoclonal antibody products for in vivo use; and therapeutic recombinant DNA-derived products. For additional information on changes to an approved application for specified biotechnology and specified synthetic biological products, see Ref. 5.

This guidance also does not apply to human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated solely under section 361 of the PHS Act (42 U.S.C. 264), as described in 21 CFR Part 1271.

This guidance does not apply to changes to an applicant's name. Such submissions are handled separately as product correspondence, in accordance with established procedures. For example, see CBER's Standard Operating Policy and Procedure (SOPP) 8403: Issuance and Reissuance of Licenses for Biological Products for further information on name changes.[5]

Some manufacturing changes discussed in this guidance may also require revision of the approved labeling (Ref. 6). Such changes are outside the scope of this guidance. In general, under 21 CFR 601.12(f):

- Labeling changes requiring supplement submission and FDA approval before distribution of the product with the labeling change include any change in the package insert, package label, or container label, including information required under 21 CFR 201.57(a), or, if applicable a Medication Guide required under 21 CFR Part 208, except those described in 21 CFR 601.12(f)(2) and (3);[6]

- Labeling changes that require supplement submission and FDA approval, but which do not require FDA approval of the supplement before the product with the labeling change may be distributed, include certain safety-related labeling changes to the package insert, package label, or container label to reflect newly acquired information, or any other labeling change that FDA specifically requests to be submitted in a changes being effected supplement under 21 CFR 601.12(f)(2)(i)(E);[7] and

- Labeling changes requiring submission in an annual report include changes to any final printed package insert, package label, container label, or Medication Guide required under 21 CFR Part 208 include, among other things, editorial or similar minor changes and changes in the information on how the product is supplied that does not involve a change in the dosage strength or dosage form.[8]

For manufacturing changes that impact labeling, reporting classification is generally commensurate with the risks of the manufacturing change. If the reporting classification recommendations are unclear for submissions that include both manufacturing and labeling changes, license holders are advised to consult with the appropriate FDA Review Division.

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[5] https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm073468.htm.

[6] 21 CFR 601.12(f)(1).

[7] 21 CFR 601.12(f)(2).

[8] 21 CFR 601.12(f)(3).

IV. REPORTING CHANGES

A. Reporting Categories

Under 21 CFR 601.12, each post-approval change in the product, production process, quality controls, equipment, facilities, responsible personnel, or labeling established in the approved BLA must be reported using the submission type associated with one of the three tier-based reporting categories depending upon the potential (i.e., risk) of the change to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product (i.e., a substantial potential, moderate potential, or minimal potential). The reporting categories in this regulatory provision also specify when the product made using the change can be distributed. The submission types associated with each reporting category are the following:

1. **Prior Approval Supplement** (PAS) - Changes that have a substantial potential to have an adverse effect on product quality (i.e., major changes) require an applicant to report the change to the FDA in a supplement to the approved BLA. A PAS must be approved by the FDA prior to distribution of the product manufactured using the change (21 CFR 601.12(b)).

2. **Changes Being Effected in 30 Days/Changes Being Effected Supplements**[9] (CBE30/CBE) - Changes that have a moderate potential to have an adverse effect on product quality (i.e., moderate changes) require an applicant to report the change to the FDA in a supplement at least 30 days prior to distribution of the product made using the change (21 CFR 601.12(c). In certain circumstances, the FDA may determine that, based on the Agency's experience with a particular type of moderate change, the supplement for such a change is complete and provides the proper information and particular assurances that the change has been appropriately submitted. The product made using such a change may be distributed immediately upon receipt of the supplement by the FDA (21 CFR 601.12(c)(5)). These circumstances may include substantial similarity with a type of change that ordinarily involves a CBE supplement or a situation in which the applicant presents evidence that the change has been validated in accordance with an approved comparability protocol (CP) under 21 CFR 601.12(e) and 21 CFR 601.12(c).

3. **Annual Report** (AR) - Changes that have a minimal potential to have an adverse effect on product quality (i.e., minor changes) shall be documented by the applicant in an annual report (21 CFR 601.12(d)).

[9] This paragraph refers to CBE supplements submitted under 21 CFR 601.12(c), and does not refer to CBE supplements for certain types of labeling changes submitted under 21 CFR 601.12(f)(2).

B. Assessing and Implementing Manufacturing Changes

1. Applicant Assessment and Implementation of Change

The potential for a change to impact product quality as it may relate to the safety or effectiveness of the product should be thoroughly assessed and documented. The information and data to demonstrate comparability of the product pre- and post-change can include a combination of testing, validation studies, and non-clinical or clinical studies as necessary to evaluate potential effects of the change. Knowledge and experience accumulated during development and commercial manufacturing regarding how product performance relates to material attributes and process parameters is useful in assessing the impact of manufacturing changes (Ref. 7). When assessing the impact of a change on product quality, some or all of the following considerations should be taken into account by the applicant:

- Prior knowledge (e.g., established chemical and biological engineering principles, published, peer-reviewed scientific and technical literature, and applied manufacturing experience) (Ref. 14);
- Development and manufacturing of the drug substance[10] (Ref. 8);
- Process validation activities and experience gained during commercial manufacture;
- Quality risk management activities; and
- Studies conducted at less than commercial scale to gain an increased understanding of the effects of the change on product quality and process consistency.

An integral component in successfully implementing any manufacturing change is an effectively-designed and effectively-managed change management process (Ref. 7). This requires an effective multidisciplinary team to implement the change and to evaluate the potential effects of the change on the product. Implementation of a change also requires oversight by the manufacturer's Quality Control Unit, and includes the studies and data to support the change approved by the applicant.

The applicant may choose to take advantage of opportunities to reduce the potential risks associated with implementing a manufacturing change. The development of robust manufacturing processes[11] and process controls that utilize innovative approaches to process validation and analytical testing provides an important component for the manufacture of high-quality products and may mitigate the risks associated with manufacturing changes. Product and process knowledge and understanding gained during development and commercial manufacturing provide a foundation for an informed change management process (Refs. 7 and 8). Thoroughly

[10] For the purposes of this document, "Drug Substance" also refers to "In vitro Substance".

[11] Process robustness is defined as an ability of a process to tolerate variability of materials and changes of the process and equipment without a negative impact on quality (Ref. 8).

characterized products, processes, and components can provide meaningful acceptance criteria and limits that assist in evaluating the potential impact of the change and reduce the risk of an unintended outcome occurring as a result of a manufacturing change.

An effective quality risk management system can enable the applicant to make informed decisions regarding manufacturing changes and permit the FDA to have greater confidence regarding the applicant's/manufacturer's ability to assure product quality and process consistency while continuously monitoring, verifying, and, as appropriate, acting upon identified risks (Ref. 3). Conducting and submitting to the FDA formal or informal risk assessments in support of a post-approval manufacturing change can allow the FDA to conduct a more effective assessment of the impact of a change, thereby facilitating timely review and decision.

2. FDA Assessment of Change

Based upon an initial assessment of the submission by the Agency, the applicant may be notified that the manufacturing change falls into a higher or lower reporting category than was proposed by the applicant. In those cases, the applicant must comply with the distribution requirements associated with the new reporting category (21 CFR 601.12(a)(2).

In some circumstances, the applicant may request an expedited review of a PAS for public health reasons or if a delay in making the described change would impose an extraordinary hardship on the applicant.[12] This expedited approach is not intended to compensate for an ineffective change management process by the applicant/manufacturer, but should be requested in situations that warrant its use, such as unexpected circumstances or product shortage.[13]

For most supplements, the CGMP status of the manufacturer's applicable product(s) and establishment(s) must be determined before the Agency renders a final decision regarding the approvability of a supplement (21 CFR 601.20). Compliance with the CGMP regulations and statutory requirements are required regardless of how the change is reported to the Agency. Moreover, it is incumbent upon the applicant to ensure that contract manufacturing and testing sites have a satisfactory CGMP status for the type of operation involved. CGMP requirements include establishing and following appropriate written procedures reviewed and approved by the Quality Control Unit, qualifying equipment as suitable for its intended use, using validated

[12] 21 CFR 601.12(b)(4).

[13] If the applicant is requesting an expedited review due to potential product shortage, for public health reasons, or for other extraordinary hardship reasons, the applicant should mark the supplement and mailing cover with "Prior Approval Supplement – Expedited Review Requested." In the case of a potential drug shortage, the applicant should also notify the FDA Drug Shortage Staff or the CBER Product Shortage Coordinator.

test methods, and ensuring the manufacturing process is under control.[14] When deemed necessary, the Agency may conduct an inspection as part of the complete review of a submission supporting the change.[15]

C. Submission of Changes to FDA

The applicant should prominently label each submission with the reporting category under which the change is being reported, provide a description of the change, as well as data to demonstrate comparability of pre-change and post-change intermediates, drug substance, and/or drug products, as appropriate, for the type of change and the reporting category. Refer to the guidances for industry on chemistry, manufacturing and controls information for specific product class content information to consider in evaluating and submitting information (Refs. 9 through 12), where applicable/available.

A submission describing the change(s) should contain all the required and expected information (i.e., descriptive narrative and appropriate data) to support the approval of the change(s) in the submission. The submission should be well organized to facilitate timely review by the FDA (Ref. 13).

An applicant is to include the following information in any supplement (PAS, CBE30, or CBE)[16]:

- A detailed description of, including a rationale for, the change;
- The product(s) involved;
- The manufacturing site(s) or area(s) affected;
- A description of the method(s) used and studies performed to evaluate the effects of the change on the product quality, and data derived from these studies;
- Relevant validation protocols and data; and
- A reference list of relevant standard operating procedures (SOPs).

An applicant is to include the following information in an Annual Report[17]:

- A list of all products involved in the change;
- A full description of and rationale for the implemented changes including:
    - the manufacturing site(s) or area(s) involved;
    - the date the change was implemented;
    - a cross-reference to relevant validation protocols and/or SOP's;
    - relevant data from studies and tests performed to evaluate the effects of the change on product quality; and

[14] 21 CFR Parts 210 and 211.

[15] The authority for FDA to conduct establishment inspections is included in both the FD&C Act and the PHS Act. Under section 351(c) of the PHS Act (42 U.S.C. 262(c)) and section 704 of the FD&C Act (21 U.S.C. 374), the FDA has authority to inspect any establishment where biological products are manufactured.

[16] Itemized information must be provided in all supplements under 21 CFR 601.12(b) and (c). This paragraph does not apply to CBE supplements for certain types of labeling changes submitted under 21 CFR 601.12(f)(2).

[17] Itemized information must be provided in an annual report under 21 CFR 601.12(d).

- A statement by the holder of the approved application or license that the effects of the change have been assessed.

D. Comparability Protocols

A CP is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC change(s) on product quality. An applicant has the option to submit one or more CPs describing the specific tests, validation studies, and acceptance criteria to be achieved in order to demonstrate the lack of adverse effect(s) for specified types of manufacturing changes on product quality. A CP, or a change to a CP, shall be submitted as a PAS (a major change) requiring approval from the FDA before distribution of a product made using the change outlined in the protocol. If approved, the CP may justify a less burdensome reporting category for the particular change (Ref. 14).[18]

A CP may be submitted for a single or multiple related changes, and may cover a single or multiple BLAs (i.e., a trans-BLA). Submission and approval of a CP may enable:

(1) greater predictability regarding the timing of implementation of CMC changes;
(2) placing the product into distribution sooner than without the use of a protocol; and
(3) more effective planning of the product supply chain.

E. Recommendations for Reporting Categories

The FDA reviews manufacturing changes reported across licensed biological products within the scope of this guidance using the tiered reporting system[19] described in section IV.A. of this guidance.

In the Appendix of this guidance, a table of frequent manufacturing changes and recommended reporting categories is provided. It is meant to serve as a guide to assist applicants and the FDA to identify reportable post-approval changes and determine appropriate reporting categories. It is based, in part, upon our overall assessment of the potential risks to process performance and product quality caused by the change. This assessment is supported by the Agency's accumulated experience resulting from inspections and reviews of post-approval manufacturing changes. The recommendations for reporting categories provided in the Appendix should be read to determine the appropriate category for the specific manufacturing change(s) under consideration. This table does not represent an exhaustive list of possible reportable manufacturing changes; a manufacturing change may still be considered reportable even if not listed in the table.

Although the selection of a reporting category for a change should be made in accordance with existing regulations and the recommendations provided in this guidance, a different selection may in some instances be deemed appropriate following discussion with the FDA. The Agency will make a decision regarding the reporting category based upon the

[18] 21 CFR 601.12(e).
[19] 21 CFR 601.12.

demonstrated robustness of the applicant's pharmaceutical or device quality system, the applicant's ability to assure process performance and the applicant's ability to mitigate risks of unintended outcomes to process performance and product quality. Early consultation with the FDA is recommended to determine the appropriate reporting category for manufacturing change(s) not described in the table in the Appendix, or when considering an adjustment to the recommended reporting categories.

Some manufacturing changes may be reported in multiple categories, depending upon the type and extent of the change and its potential effects. When considering the correct reporting category for a submission, the applicant should ensure that the highest-risk change determines the reporting category that is chosen for the submission. For example, there may be several moderate-risk changes associated with one major-risk change, in which case the reporting category for the highest risk (e.g., PAS) may be an appropriate choice for the submission.

When multiple changes are made to a process, it may be appropriate to consider the cumulative impact of all changes, which may lead to a higher reporting category.

We recommend, if an applicant includes multiple changes in one supplement, that all of the changes in the supplement be somehow related, or pertain to a similar step in the manufacture (e.g., changes associated with an increase in a production scale, or multiple changes made to a purification process). While the inclusion of multiple related changes in one supplement may result in a higher reporting category proportionate to the change with the highest risk as well as cumulative impact of all changes, this approach is expected to provide a comprehensive assessment of the combined effect of all changes on process performance and product quality. Inclusion of multiple unrelated changes in one submission, even those in the same reporting category, could result in a potential delay in implementing all of the changes (e.g., approvability of any single change may affect approvability of all the changes included in the supplement).

F. Implementing Changes to Approved Established Conditions

Established Conditions are defined by the FDA 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 Established Conditions must be reported to the FDA in a post-approval regulatory submission following the reporting classification recommendations provided in this guidance, or as agreed upon with the appropriate FDA Review Division at the time of approval.[20] Changes to aspects of chemistry, manufacturing, and controls determined not to be Established Conditions generally do not require regulatory reporting, unless deemed otherwise by the FDA at which point such a change would be reverted to an Established Condition or be reported by the applicant on a voluntary basis. For more information on how to identify, monitor, and manage

[20] 21 CFR 601.12.

Established Conditions and aspects of chemistry, manufacturing, and controls determined not to be Established Conditions, refer to pertinent guidances (Ref. 15) and/or consult with the appropriate FDA Review Division.

V. SPECIAL CONSIDERATIONS

A. Change in Process Parameters

Process parameters (operating and performance) are frequently adjusted over a product's lifecycle. Additional knowledge and experience about material attributes (e.g., starting materials, raw materials, reagents, solvents, etc.), operating and performance parameters, and the way their interaction affects product quality and process performance typically enables a more informed risk assessment and risk ranking. Any change to process parameters (operating or performance) outside of an approved validated range(s) should be evaluated with respect to criticality, impact on process performance and product quality, and effectiveness of the overall control strategy and must be reported to FDA.[21] The reporting category selected should be commensurate with the risk of an unintended outcome resulting from changes involving these elements.

B. Change in a Supplier of Raw Materials

We recommend the following manufacturing changes be reported in a PAS:

1. A change in a supplier of raw materials that have a substantial potential to affect product quality, including inactivation, detoxification, immunization in the production of hyperimmune plasma, or conjugation (e.g., PEG, acridinium ester, biotin, beads); and
2. A change in a supplier of raw materials that have a substantial potential to affect product quality, including an ability to maintain specified pH or ionic strength in the manufacture of plasma-derived fractionated products (e.g., phosphate, tris, ethanol).

We recommend the following manufacturing changes be reported in a CBE30:

1. A change in a supplier of raw materials used to aid in filtration (e.g., celite, diatomaceous earth, activated carbon);
2. A change in a supplier of trypsin or serum used in the manufacture of viral vaccine products.

[21] 21 CFR 601.12

We recommend the following manufacturing change be reported in an AR or be controlled under a firm's pharmaceutical/device quality system, as appropriate:

A change in a supplier of raw materials, reagents, and solvents that have a minimal potential to affect product quality, provided that the materials' specific use, physicochemical properties, impurity content, and acceptance criteria remain unchanged.

VI. GLOSSARY

Acceptance Criteria - Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the Drug Substance or Drug Product or materials at other stages of their manufacture should meet. (Ref. 16)

Adventitious Agent - A microorganism (including bacterium, fungus, mycoplasma/spiroplasma, mycobacterium, rickettsia, virus, protozoa, parasite, Transmissible Spongiform Encephalopathy (TSE) agent) that is inadvertently introduced into the production of a biological product. (Ref. 17)

Analytical Procedure - Refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include, but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, and use of the formulae for the calculation. (Ref. 25)

Analytical Technique/Methodology - Refers to a general principle/mechanism of operation upon which an analytical procedure is based (e.g., Reverse Phase High Performance Liquid Chromatography, Near Infrared Spectroscopy, Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis, Analytical Ultracentrifugation, etc.).

Analytical Test - A measure of a specific attribute (e.g., identity, purity, potency, strength).

Comparability Protocol (CP) - A comprehensive, prospectively written plan for assessing the effect of a proposed CMC change(s) on the identity, strength, quality, purity, and potency of a drug product or a biological product (including an IVD), as these factors may relate to the safety or effectiveness of the product. The CP describes the specific tests and studies to be performed and the acceptance criteria to be achieved to demonstrate the lack of adverse effect(s) of one or more proposed CMC changes on product quality. (Ref. 14)

Container Closure System (CCS) - The sum of packaging components that together contain and protect the dosage form (Drug Product). The CCS includes primary packaging components; it can also include secondary packaging components, if these are intended to provide additional protection to the Drug Product. A packaging system is equivalent to a container/closure system. (Ref. 18)

Control Strategy - A planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (Ref. 7)

Device Quality System Regulation (QSR) - Means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.
(see 21 CFR Part 820).

Establishment - A place of business under one management at one general physical location. The term includes, among others, independent laboratories that engage in control activities for a registered drug establishment (e.g., consulting laboratories), blood donor centers, and animal facilities-used for the production or control testing of licensed biologicals. (see 21 CFR 207.1)

Excipient (an inactive ingredient) - An ingredient added intentionally to the drug substance which should not have pharmacological properties in the quantity used. (Ref. 16)

In-house Primary Reference Material - An appropriately-characterized material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which an in-house working reference material is calibrated. (Ref. 16)

In-house Working Reference Material - A material prepared similarly to the in-house primary reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is calibrated against the in-house primary reference material. (Ref. 16)

In vitro Product - The licensed product in its final form and all assembled supporting components. (Ref. 10)

In vitro Substance - Any and all raw materials and intermediates used in the manufacture of the final in vitro product as defined in 21 CFR 820.3(c). (Ref. 10)

Location - All buildings, appurtenances, equipment and animals used, and personnel engaged by a manufacturer within a particular area designated by an address adequate for identification.
(see 21 CFR 600.3(v))

Master Cell Bank (MCB) - An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks. (Ref. 19)

Master Virus Seed - A viral seed of a selected vaccine virus from which all future vaccine production will be derived, either directly or via Working Virus Seeds. (Ref. 17)

Manufacture - Each step in the manufacture, preparation, propagation, compounding, or processing of a drug. Manufacture includes the making by chemical, physical, biological, or other procedures or manipulations of a drug, including control procedures applied to the final product or to any part of the process. Manufacture includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process, including, for example, analytical testing of drugs for another registered establishment's drug. (see 21 CFR 207.1).

Method Performance - The ability of a procedure to fulfill the type and level of characteristics appropriate for its intended use (e.g., accuracy, specificity, precision).

Packaging - A *packaging component* means any single part of a CCS. Typical components are containers (e.g., ampules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper over seals, container inner seals, administration ports (e.g., on large-volume parenterals (LVPs)), overwraps, administration accessories, and container labels. A *primary packaging component* means a packaging component that is or may be in direct contact with the dosage form. A *secondary packaging component* means a packaging component that is not and will not be in direct contact with the dosage form. (Ref. 18)

Pharmaceutical Quality System (PQS) - A management system to direct and control a pharmaceutical company with regard to quality. The PQS includes the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management to ensure continual improvement. (Refs. 7 and 21)

Process Step (Unit Operation) - A discrete manufacturing activity or manipulation that achieves a specific process objective (e.g., cell culture/fermentation, filtration, centrifugation, inactivation, holding, chromatography (e.g., specific column), packaging, labeling, chemical modification).

Process Parameters:

Operating Parameter - A condition of the manufacturing process that can be directly controlled. Typically, these parameters are physical or chemical (e.g., temperature, process time, column flow rate, column wash volume, reagent concentration, or buffer pH). (Ref. 20)

Performance Parameter - A characteristic of the process that provides assurance of consistency and quality.

Raw Material:

Biological Raw Material - Raw material from a biological source (e.g., animal, human or plant), which is intended to be used as a processing aid in the manufacture of a

biological product. It may be absent from the final product or may remain as an impurity in the final product at the end of the manufacturing process (e.g., biological additives used to supplement cell culture medium in production fermenter, human antithrombin III used to complex and remove human thrombin, etc.). (Modified from Ref. 22)

Reference Material - See In-house Primary Reference Material and In-house Working Reference Material.

Reference Standard - An international or national standard used to calculate the units of activity in a biological assay and to calibrate the in-house reference material. (Ref. 16)

Reprocessing - Subjecting an in-process material, Drug Substance or Drug Product, including one that does not conform to predetermined specifications to a previous step in the validated manufacturing process in order to obtain acceptable quality in-process material, Drug Substance or Drug Product. (Modified from Ref. 20)

Reworking - Subjecting an in-process material, Drug Substance or Drug Product that does not conform to predetermined specification to one or more processing steps that are different from the established manufacturing process in order to obtain acceptable quality in-process material, Drug Substance or Drug Product. In general, reworking operations are developed post-approval, and the application is updated through submission of a PAS. (Modified from Ref. 20)

Specification - The quality standards (i.e., tests, analytical procedures and acceptance criteria) provided in an approved application to confirm the quality of products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a product. (see 21 CFR 600.3(kk)). Term "test" is defined as "Analytical Test" in alphabetical order above; terms "Analytical Procedure" and "Acceptance Criteria" are likewise defined in alphabetical order above.

Starting Material (**or Source Material**) - For the purposes of this document term Starting Material (or source material) is the same as Biological Starting Material - Material from a biological source which is intended to be used in manufacture of a biologic product and from which the active ingredient is derived either directly (e.g., plasma derivatives, ascetic fluid, bovine lung,) or indirectly (e.g., cell substrate, host/vector production cells, eggs, viral strains). (Modified from Ref. 22)

Viral Clearance - Elimination of target virus by removal of viral particles or inactivation of viral infectivity. (Ref. 23)

Working Cell Bank/Working Virus Seed - Cell/virus bank prepared from aliquots of a homogenous suspension of cells/viruses derived from culturing the Master Cell Bank/Master Virus Seed under defined culture conditions. (Ref. 19)

VII. REFERENCES

1. Changes to an Approved Application; Final rule (62 FR 39890, July 24, 1997). https://www.gpo.gov/fdsys/pkg/FR-1997-07-24/pdf/97-19427.pdf
2. Supplements and Other Changes to an Approved Application; Final rule (69 FR 18728, April 8, 2004). https://www.gpo.gov/fdsys/pkg/FR-2004-04-08/pdf/04-7532.pdf
3. Guidance for Industry: Q9 Quality Risk Management, June 2006. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073511.pdf
4. Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, December 2014. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM354668.pdf
5. Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products, July 1997. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm124805.pdf
6. Guidance for Industry: Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements, February 2013. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm075082.pdf
7. Guidance for Industry: Q10 Pharmaceutical Quality System, April 2009. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073517.pdf
8. Guidance for Industry: Q11 Development and Manufacture of Drug Substances, November 2012. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm261078.pdf
9. Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Plasma-Derived Biological Products, Animal Plasma or Serum-Derived Products, February 1999. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm080825.pdf
10. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for Biological *In Vitro* Diagnostic Product, March 1999. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm080819.pdf
11. Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for Vaccine or Related Product, January 1999. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092272.pdf

12. Guidance for Industry: On the Content and Format of Chemistry, Manufacturing, and Controls Information and Establishment Description Information for an Allergenic Extract or Allergen Patch Test, April 1999. https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Allergenics/ucm078638.pdf
13. Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products, April 2005. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm079748.pdf
14. Draft Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information, April 2016.* https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm496611.pdf
15. Draft Guidance for Industry: Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products, May 2015.* https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm448638.pdf
16. Guidance for Industry: Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products, April 1999. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073488.pdf
17. Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications, February 2010. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM202439.pdf
18. Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Documentation, May 1999. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm070551.pdf
19. Q5D Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products, September 1998. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073471.pdf
20. Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients; Guidance for Industry, September 2016. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073497.pdf
21. Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations, September 2006. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm070337.pdf

22. Guidance Document: Post – Notice of Compliance (NOC) Changes: Quality Document, Government of Canada, September 2009. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/post-notice-compliance-changes/quality-document.html
23. Guidance for Industry: Q5A Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin, September 1998. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073454.pdf
24. ICH Harmonised Tripartite Guideline: The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q(R1), September 2002. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q__R1_.pdf
25. ICH Harmonised Tripartite Guideline: Validation of Analytical Procedures: Text and Methodology: Q2(R1), November 2005. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

***** When finalized, this guidance will represent the Agency's current thinking on this topic.

APPENDIX

Examples of Post-Approval Manufacturing Changes and Recommended Reporting Categories

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
3.2.S. DRUG SUBSTANCE[22] (Ref. 24)		
3.2.S.2. Manufacture		
3.2.S.2.2 Description of Manufacturing Process and Process Controls		
Change in unit operations and their sequence including addition, deletion, or substitution of unit operation(s). NOTE: This change applies both to upstream steps of Drug Substance manufacture through harvesting and downstream purification steps.		
Changes to the Upstream Steps of Drug Substance Manufacture through Harvesting		
Change in the growth culture conditions (e.g., time, temperature, pH, etc.) and/or media composition outside of the parameters specified in the approved BLA.		

[22] For the purposes of this document, "Drug Substance" also refers to "In vitro Substance".

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Change in a batch size (increase or decrease)		Change in fermentation step batch size (e.g., minor adjustments in volume) using the same equipment with no change in process parameters, controls and specifications.
Change in the production capacity for concurrent manufacturing processes by addition of identical unit processes (an increase in throughput). NOTE: This applies only to cellular and cell-based gene therapy products.	Addition of a duplicated cell culture process train with no change in process parameters specified in the approved BLA. NOTE: This does not apply to cellular and cell-based gene therapy products.	Change in the production scale (increase or decrease) of ancillary equipment (e.g., media tanks, buffer tanks, etc.) with no direct product contact and no change in process parameters specified in the approved BLA.
		Change in the harvesting and/or pooling procedures that does not affect the method of manufacture, recovery, storage conditions, production scale or sensitivity of detection of adventitious agents NOTE: This does not apply to cellular therapy and cell-based gene therapy products.

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Change from a stainless steel to disposable (e.g., bag) bioreactor or vice versa. NOTE: This information may be provided in 3.2.S.2.2 and/or 3.2.A.1		
Change in the Drug Substance Purification Process		
Change in a batch size (increase or decrease) by changing the size of purification/inactivation equipment. NOTE: This information may be provided in 3.2.S.2.2 and/or 3.2.A.1	Addition of duplicated process train or process step(s) (e.g., bioreactor/fermenter, purification/inactivation, etc.) with no change in the process parameters specified in the approved license.	
Increase in the number of cycles of resin and membrane re-use without an approved protocol.	Change in the filter or resin supplier with no change in the resin material, operating or performance parameters.	Increase in the number of cycles of resin and membrane re-use according to an approved protocol.
	Addition of a bioburden reduction or clarifying filter.	
A change in the composition or formulation (e.g., pH, ionic strength, molarity, etc.) of solutions (buffers, reagents, etc.) used in processing.		
New or revised purification process (e.g., change in the resin or filter material, loading scale, column size, or elution rate of a chromatographic column).		

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Change in the method(s) for virus or adventitious agent removal or inactivation. NOTE: This information may be provided in 3.2.S.2.2 and/or 3.2.S.2.3		
Reprocessing in the manufacture of a Drug Substance without an approved protocol.		Reprocessing in the manufacture of a Drug Substance with an approved protocol.
Reworking in the manufacture of a Drug Substance.		
3.2.S.2.3 Control of Materials		
Changes to the source of starting materials and raw materials		
Change in a source of starting material. NOTE: This type of change may in some instances (e.g., from tissue or plasma-derived to recombinant, from animal to plant, etc.) result in a separate BLA. Applicants should discuss with the appropriate FDA Review Division to determine the appropriate reporting category.		
Change in a source of a biological raw material (e.g., animal, human, or plant).		

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Adding a new source of pancreatic tissue outside of the approved region. NOTE: This does not apply to cellular therapy products isolated from pancreatic tissue.		Adding a new source of pancreatic tissue within the approved region.
Changes to the cell banks/cell seeds		
Generation of a new master cell bank or master virus seed from a source material or cell line using the same or different expression construct. NOTE: This does not apply to gene therapy products.	For cellular therapy products and cell-based gene therapy products, generation of a cell bank from cells/tissues of a new human donor according to a protocol specified in the approved BLA.	
Generation of a working cell bank or working seed from an approved master cell bank or master virus seed according to a new protocol not specified in the approved BLA.		Generation of a working cell bank or seed from an approved master cell bank or master virus seed according to a protocol specified in the approved BLA.
Change in an approved protocol for qualification of master/working cell bank or master/working seed.		
Extension of the shelf life of cell banks or cell seeds used in the manufacture of cellular therapy, viral and bacterial vaccine products.		

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
3.2.S.2.4 Controls of Critical Steps and Intermediates		
Change in the process parameter(s) monitored at critical steps of the manufacturing process identified in 3.2.S.2.2 outside of the range validated in the approved BLA. NOTE: For additional guidance how to determine (critical) process parameters see section V. SPECIAL CONSIDERATIONS, A. Change in Process Parameters).		
Change in the procedure used for conjugation reaction (e.g., incubation time, temperature, concentration of the starting materials, etc.).		
Change in the procedure used for inactivation or detoxification (e.g., incubation time, temperature, type and amount of materials used, etc.). NOTE: Applies only to vaccine products for changes to Drug Substance manufacture and purification.		

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Change in the Container Closure System (CCS) used for storage and/or shipping of a stored intermediate that includes a change in the product-contact material or dimensions (size and shape).		Change in the CCS used for storage and/or shipping of a stored intermediate with no change in the product-contact material or dimensions (size and shape).
3.2.S.4. CONTROL OF DRUG SUBSTANCE ***(also applies to 3.2.P.5 CONTROL OF DRUG PRODUCT)***		
Change in the Drug Substance or Drug Product release specifications including: • Adding, deleting, or replacing a test(s). • Adding, deleting, broadening or shifting the approved acceptance criteria. • Replacing or modifying an approved analytical procedure resulting in a change in analytical technique/methodology, acceptance criteria or method performance.	Relaxation of acceptance criteria to comply with a compendial test approved in the BLA that is consistent with FDA statutory and regulatory authority (21 CFR 601.12(c)(2)(iv)).	Tightening of an approved acceptance criterion due to improved process or assay performance. NOTE: If tightening is in response to mitigating safety risks, or if the product is unable to meet the new limits possibly leading to drug shortage, the applicant should consult appropriate FDA Review Division.
		Minor modifications to an approved analytical procedure with no change in the analytical technique/methodology, acceptance criteria, and method performance.

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Replacing critical test control(s) or reagents (e.g., positive controls, capture antibodies, etc.) without an approved protocol.		Replacing critical test control(s) or reagents (e.g., positive controls, capture antibodies, etc.) according to an approved protocol.
		Any change made to comply with a change to an official compendium, except for relaxation of acceptance criteria or deletion of a test, that is consistent with FDA statutory and regulatory requirements.
3.2.S.5. REFERENCE STANDARDS OR MATERIALS USED TO RELEASE DRUG SUBSTANCE ***(also applies to 3.2.P.6. REFERENCE STANDARDS OR MATERIALS USED TO RELEASE DRUG PRODUCT)***		
Changing to a new lot of, new source for, or different, in-house reference material or reference panel (panel member) without an approved protocol.		Changing to a new lot of, new source for, or different, in-house reference material or reference panel (panel member) according to an approved protocol.
Changing from a national or international reference standard to an in-house reference material and vice versa.		
Changing from a national to an international reference standard and vice versa. NOTE: This applies only to vaccine, and cellular and gene therapy products.		Changing to an alternative national or international reference standard or reference panel without a change in the acceptance criteria.

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
		NOTE: This does not apply to vaccine, and cellular and gene therapy products.
Changing an approved protocol to qualify an in-house reference material.		Tightening of the acceptance criteria of an in-house reference material.
Extension of the shelf-life of an in-house reference material without an approved protocol.		Extension of the shelf-life of an in-house reference material according to an approved protocol.
3.2.S.6. CONTAINER CLOSURE SYSTEM FOR DRUG SUBSTANCE		
Adding or replacing a primary CCS for storage and/or shipping of Drug Substance including a change in the product-contact material or dimensions (size and shape).		Change in a supplier of a primary CCS (other than disposable bag) with no change in the product-contact material.
Adding or replacing a primary CCS for storage and/or shipping of lyophilized Drug Substance.		Change in a primary CCS for storage and shipping of a bioburden-controlled Drug Substance with no change in the product-contact material and dimensions (size and shape).
Change in the container closure integrity test, or an analytical procedure to demonstrate container closure integrity, of a primary CCS for storage and shipping of sterile Drug Substance.		

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Change in the shipping conditions (e.g., temperature, duration, packaging, etc.) without an approved shipping protocol.		Change in the shipping conditions (e.g., temperature, duration, packaging, etc.) based on an approved shipping protocol.
3.2.S.7. STABILITY ***(also applies to 3.2.P.8. DRUG PRODUCT STABILITY)***		
Extension of a shelf life without an approved protocol, or a change in the storage conditions (e.g., temperature, humidity, orientation, etc.) for Drug Substance, Drug Product or a stored intermediate.		Extension of a shelf life based upon full shelf life data on commercial batches and a protocol that is approved for this specific purpose.
Change in the post-approval stability protocol or stability commitment (3.2.S.7.2 and 3.2.P.8.2) including: • deletion, replacement or change in stability specifications. • change in storage conditions (e.g., temperature, humidity, orientation, etc.). • deletion of time point(s) within the approved shelf life.		Change in the stability protocol to include more stringent parameters (e.g., tightened acceptance criteria or additional time points). NOTE: If tightening is in response to mitigating safety risks, or if the product is unable to meet the new limits, which could possibly lead to drug shortage, the applicant should consult appropriate FDA Review Division.

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
3.2.P. DRUG PRODUCT[23]		
3.2.P.1. Description and Composition of the Drug Product		
Addition or replacement (e.g., liquid to lyophilized) of a dosage form.		
	Change in the fill volume.	
Addition of a strength.		
Change (e.g., new manufacturer, new location, new filling line, change in sterilization method/cycle) in the diluent co-packaged with the product. NOTE: This does not apply to convenience kits or commercially available diluents.		
Change in a type or concentration of preservative.		
Addition of a new presentation (e.g., addition of prefilled syringe to vial).		

[23] For the purposes of this document, "Drug Product" also refers to "In vitro Product".

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Deletion or reduction of an ingredient intended only to affect the color of the Blood Grouping Reagents. (21 CFR 601.12(d)(2)(ii))		Deletion or reduction of an ingredient intended only to affect the color of the product. NOTE: If a change is intended only to affect the color of Blood Grouping Reagents, the applicant must submit a PAS, and FDA approval of the change is required prior to distribution of the product made using the change. (21 CFR 601.12(d)(2)(ii))
3.2.P.3. MANUFACTURE		
3.2.P.3.3 Description of Manufacturing Process and Process Controls		
Change in unit operations and their sequence, including addition, deletion, or substitution of unit operation(s).		
Scale-up of the manufacturing process at the formulation/filling/lyophilization stage.		
Reprocessing in the manufacture of Drug Product without an approved reprocessing protocol.		Reprocessing in the manufacture of Drug Product with an approved reprocessing protocol.
Reworking in the manufacture of Drug Product.		

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
3.2.P.3.4 Controls of Critical Steps and Intermediates		
Change in the process parameter(s) monitored at critical steps of the manufacturing process identified in 3.2.P.3.3 outside of the validated range in the approved BLA. NOTE: For additional guidance how to determine (critical) process parameters see section V. SPECIAL CONSIDERATIONS, A. Change in Process Parameters.		
Change in the CCS used for storage and/or shipping of a stored intermediate that includes a change in the product-contact material or dimensions (size and shape).		Change in the CCS used for storage and/or shipping of a stored intermediate with no change in the product-contact material or dimensions (size and shape).
3.2.P.4. CONTROL OF EXCIPIENTS		
Change in the composition or concentration of excipients.		
Change in the source of an excipient to one that carries risk for Transmissible Spongiform Encephalopathy (TSE) (i.e., plant or synthetic to animal).	Change in the source of an excipient that eliminates the risk for TSE (i.e., animal to plant or synthetic).	

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
		Change in the supplier of an excipient with no change in the source.
3.2.P.5. CONTROL OF DRUG PRODUCT ***(See Section 3.2.S.4. CONTROL OF DRUG SUBSTANCE)***		
3.2.P.6. REFERENCE STANDARDS OR MATERIALS USED TO RELEASE DRUG PRODUCT ***(See Section 3.2.S.5. REFERENCE STANDARDS OR MATERIALS USED TO RELEASE DRUG SUBSTANCE)***		
3.2.P.7. CONTAINER CLOSURE SYSTEM FOR DRUG PRODUCT		
Adding or replacing a primary CCS for storage of Drug Product including a change in the product-contact material or dimensions (size and shape).		Deleting a CCS when multiple CCS have been approved. NOTE: If the change also impacts the labeling, inquire with an appropriate FDA Review Division regarding the reporting classification.

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Adding or replacing a supplier for components of the CCS that are supplied as ready-to-use or ready-to-sterilize with or without a change in the product-contact material or dimensions (size and shape).	Adding or replacing location that performs depyrogenation or sterilization for components of the CCS that are supplied as ready-to-use or ready-to-sterilize without a change in supplier, product-contact material, or dimensions (size and shape).	Adding or replacing a supplier of a primary CCS with no change in the product-contact material, or dimensions (size and shape). NOTE: When changing or adding a new CCS supplier, biologic manufacturers are advised to examine the quality management program of vial manufacturers to assure appropriate selection and qualification of the incoming glass vials. The current good manufacturing practice regulations require that all final containers and closures shall be clean and free of surface solids, leachable contaminants and other materials that will hasten the deterioration of the product or otherwise render it less suitable for the intended use per 21 CFR 600.11(h).
Change in the container closure integrity, or an analytical procedure to demonstrate container closure integrity of a primary CCS for storage and shipping of Drug Product.		Change within the CCS for a nonsterile product, based upon a showing of equivalency to the approved system under a protocol approved in the application or

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
		published in an official compendium (21 CFR 601.12(d)(2)(iv)).
		Change in dimensions (size and shape) of a container containing the same number of dosage units for a nonsterile solid dosage form product, without a change from one CCS to another (21 CFR 601.12(d)(2)(v)).
		Change in the CCS for storage and shipping of Drug Product with no change in the product-contact material and dimensions (size and shape).
Change in the shipping conditions (e.g., temperature, duration, packaging, etc.) without an approved shipping protocol.		Change in the shipping conditions (e.g., temperature, duration, packaging, etc.) based on an approved shipping protocol.
		Addition by embossing, debossing, or engraving of a code imprint to a solid dosage form biological product other than a modified release dosage form, or a minor change in an existing code imprint.
		Changes to a crimp cap (ferrule and flip cap/overseal), provided

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
		that there are no changes to the color and that the container and closure integrity have been demonstrated using a validated test method.
3.2.P.8. DRUG PRODUCT STABILITY ***(See section 3.2.S.7. DRUG SUBSTANCE STABILITY)***		
FACILITIES AND EQUIPMENT NOTE: Examples of changes described in this section may be provided in the following sections of the Common Technical Document (CTD): 3.2.S.2, 3.2.P.3 and 3.2.A.1 (Ref. 24)		
EQUIPMENT		
Addition of new equipment (e.g., bioreactor/fermenter, purification/inactivation, etc.) that results in a change in a batch size (increase or decrease) or operating parameters.	Addition of duplicated process train or process step(s) (e.g., bioreactor/fermenter, purification/inactivation etc.) with no change in the process parameters specified in the approved BLA.	Addition or replacement of equipment of the same size and material of construction used in harvesting and pooling with no change in the process parameters specified in the approved BLA.

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
	Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology, process operating parameters or aseptic processing.	
FACILITIES		
Change in the Manufacturing Location		
Addition or replacement of a manufacturing facility for production of Drug Substance, Drug Product or intermediates.		Addition of new areas used for the preparation of sterile materials/equipment for sterile product manufacture.
		Addition of packaging and/or labeling lines to an approved facility.
Addition or replacement of an existing labeling and/or packaging location(s) that does not have a CGMP status (i.e., no inspectional history).		

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Change in the Testing Location NOTE: It is incumbent upon the Applicant to ensure that contract testing locations meet CGMP requirements.		
Addition or replacement of a testing laboratory that performs critical testing with a new testing laboratory at a new location. Examples would include potency or safety testing for the final drug product.	Addition or replacement of a testing laboratory for release or stability testing by moving within an existing location.	Addition or replacement of a testing location for in-process controls with no change in the in-process control limits outside of the approved ranges.
	Addition or replacement of a testing laboratory that performs other release or stability testing not described under a PAS by moving to a new location.	
	Change in the cell/seed bank testing location with no change in the specifications used for the release of the cell/seed bank.	
Changes within a location		
Addition or replacement of an existing building for production of Drug Substance, Drug Product or intermediates within an approved manufacturing location.	Addition or replacement of an existing suite/room that does not affect sterility assurance or contamination/cross-contamination within an approved manufacturing building.	Relocation of manufacturing equipment within an approved manufacturing location to improve product/personnel/raw material flow and segregation of materials.

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Addition, expansion or replacement of a suite/room that may affect contamination or cross-contamination within an approved manufacturing building.		Change in a location or modification to areas used in support operations (e.g., preparation of buffers, media, gowning, temperature-controlled areas, upstream processing such as egg incubation and inoculation, plasma thawing and pooling, etc.).
		Installation of a new, or modification of an existing, Water for Injection (WFI) system in an approved facility. (NOTE: This information should be provided as part of a complete submission for a new facility).
		Change in the Environmental Quality Classification to a lower (less stringent) classification except for aseptic processing areas.
		Establishing new environmental monitoring levels for aseptic processing areas such as decrease in sampling points and frequency based on historical data.
		Installation of a new HVAC system or modification to an existing system to environmentally

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
		controlled areas used for process steps (e.g., cell culture, purification) except for asceptic processing areas.
Multiproduct Manufacturing		
Introduction of product(s) that represent an additional level of risk (e.g., toxic, highly potent, sensitizing, proteolytic, that represent added risks for adventitious agents or a new product class) into a manufacturing area that has not been approved for this type of manufacturing operation(s).	Introduction of product(s) into a manufacturing area using shared product contact equipment that requires change(s) to the approved and validated cleaning and changeover procedure(s) with no additional containment requirements (not described under Multiproduct Manufacturing PAS).	Introduction of product(s) into a manufacturing area using dedicated or shared product contact equipment with no changes to the approved and validated cleaning and changeover procedure(s) (not described under Multiproduct Manufacturing PAS or CBE30).
Aseptic Processing/Sterilization NOTE: Information pertaining to the product quality microbiology data, description and validation of the sterilization process, and aseptic processing should be submitted in accordance with ICH M4Q(R1) (Ref. 24)		
Transfer of manufacturing of an aseptically processed sterile Drug Substance or Drug Product into a new or renovated aseptic processing area within the currently licensed building.	Use of an alternate filling line approved for aseptic manufacture of other products with no change in the validated aseptic process and product contact equipment.	Addition or replacement of equipment used in the sterilization/depyrogenation of equipment used for processing of sterile intermediates and drug product (e.g., autoclave, new steam-in-place equipment, depyrogenation oven or tunnel, etc.) where operating parameters have not been changed.

PRIOR APPROVAL (PAS)	CHANGES BEING EFFECTED in 30 DAYS (CBE30)*	ANNUAL REPORT (AR)
Addition or modification to an approved filling line that affects sterility assurance.	Change to a final sterilization filter supplier with no change in material, dimensions or sterilization method.	
Changes that may affect product sterility assurance, such as changes in product or component sterilization method(s), or an addition, deletion or substitution of steps in an aseptic processing operation (21 CFR 601.12(b)(2)(vi)).	Addition or replacement of equipment (e.g., autoclave, new steam-in-place (SIP) equipment, depyrogenation oven or tunnel) used in the sterilization/depyrogenation of product-contact materials (e.g., vials, stoppers, etc.) and/or equipment (e.g., tanks, filling lines, etc.) used for sterile intermediates and Drug Product where operating parameters have been changed.	Addition or replacement of an autoclave for sterilization of materials used for microbiologically controlled Drug Substance or Drug Product.
Change in a membrane material or dimensions of the final sterilization filter.	Changes to sterilization cycles for sterile product contact equipment.	

*FDA recommends that the following manufacturing changes be submitted in a CBE supplement under 21 CFR 601.12(c)(5). As explained in this provision, products made using such changes may be distributed immediately upon receipt of the supplement by FDA:

- Adding limits for production intermediates without a change in the process (applicable both to sections Changes to the Upstream Steps and Drug Substance Purification).
- Change in the system suitability criteria without a change in an approved analytical procedure.
- Change in a supplier of a disposable primary container (i.e., bag) with no change in the construction material.
- Reduction in Drug Substance or Drug Product shelf life where acceptance criteria become tightened or remain unchanged (NOTE: This change may result in a higher reporting category for cellular therapy and cell-based gene therapy products with a very short shelf life. Applicants should discuss with the appropriate FDA Review Division to determine the reporting category).
- Addition or replacement of an existing labeling and/or packaging location that has a CGMP status (i.e., inspectional history).