Coalition for PET Drug Approval

Radiopharmaceutical Sciences Council

Reporting Changes to an Approved NDA or ANDA

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Disclosures

- Employee of PETNET Solutions, Inc.
- Will not discuss usages or indications for any approved and investigational agents

Learning Objectives

- Overview of the major categories for reporting post-approval changes
- Overview of the types of changes for each category
- Review specific examples of each type of change
- Review references (Guidance Documents)

Four Categories for Reporting Post-approval Changes

- Prior Approval Supplement
- Supplement – Changes being effected in 30 days (CBE-30)
- Supplement – Changes being effected immediately (CBE-0)
- Annual Report

The answer to the following question determines which reporting category is used:

What is the potential (risk) for the change to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as they may relate to the safety or effectiveness of the drug.

The answer is your risk assessment used to justify the category chosen

Prior Approval Supplement

- requires approval by FDA prior to distribution of the drug product made using the change
- used for submission of a major change

A ***major change*** is defined as having a substantial potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product

Supplement – Changes being effected in 30 days (CBE-30)

- requires submission of a supplement at least 30 days prior to distribution of the drug product made using the change
- used for submission of a moderate change

The drug product made cannot be distributed if FDA informs applicant within 30 days of receipt of the supplement that a Prior Approval supplement is required for the change

Supplement – Changes being effected immediately (CBE-0)

- does not require FDA approval prior to distribution of the drug product made using the change
- used for submission of certain types of moderate changes

If, after review, FDA disapproves the change, FDA may order the manufacturer to cease distribution of the drug product made using the change

Annual Report

- does not require FDA approval prior to distribution of the drug product made using the change
- used for submission of a minor change

A ***minor change*** is defined as having a minimal potential to have an adverse effect on the identity, strength, quality, purity or potency of a drug product

Reporting changes

- Each change should be described in enough detail in the cover letter or summary section of the Annual Report to allow FDA to determine whether the appropriate reporting category has been used.

The following information must be contained in a Prior Approval Supplement

1) A detailed description of the proposed change
2) The drug product(s) involved
3) The manufacturing site(s) or area(s) affected
4) A description of the methods used and studies performed to assess the effects of the change
5) The data derived from such studies
6) For sterilization process and test methodologies related to sterilization process validation, relevant validation protocols and a list of relevant standard operating procedures must be provided in addition to the requirements in 3) and 4)

Types of Changes for Prior Approval Supplements

1.) Changes in the qualitative or quantitative formulation of the drug product, including inactive ingredients or in the specifications

Examples:

- changes in specification of drug concentration, pH, chemical purity (EtOH, Acetonitrile, K222), NaCl concentration, BET concentration limit, deleting any part of a specification, etc.
- establishing a new analytical procedure or a change in an analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as described in the approved application

Types of Changes for Prior Approval Supplements

2.) Changes that may affect drug product sterility assurance, such as changes in drug product sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation

Examples:

- addition to an aseptic processing line of new equipment made of different materials
- deletion of equipment from an aseptic processing line
- changes in the sterilization method (e.g., filtration, chemical, irradiation)
- changes in materials or pore size rating of filters used in aseptic processing

Types of Changes for Prior Approval Supplements

3.) Changes in the manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance

Examples:

- changes in solvents (e.g., acetonitrile to tetrahydrofuran)
- changes in the precursor (e.g., mannose triflate to mannose tosylate)
- changes in the resins of the purification columns
- changes in the hydrolysis method (e.g., acid vs. base, hydrochloric acid to sulfuric acid or phosphoric acid)
- changes of the crown ether used to complex the cation

Types of Changes for Prior Approval Supplements

4.) Labeling changes

Examples:

- changes based on post-marketing study results, including, but not limited to, labeling changes associated with new indications and usage
- revision (expansion or contraction) of population based on data
- claims of superiority to another drug product

Types of Changes for Prior Approval Supplements

5.) Changes in container closure system

Examples:

- changes in a drug product container closure system that controls the drug product delivered to a patient
- changes in the type (e.g., glass to high density polyethylene (HDPE), vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of a packaging component that may affect the impurity profile of the drug product

The following information must be contained in a CBE-30 Supplement

1) Full explanation of the basis for the change
2) The date on which the change is to be made

- The applicant must wait 30 days after submission of the CBE-30 Supplement before distributing the drug product made using the change
- If the FDA informs the applicant within 30 days of the submission that any information is missing, the applicant must not distribute the drug product made using the change until the supplement has been amended to provide the missing information
- The FDA may inform the applicant that the change needs to be re-submitted as a Prior Approval Supplement

Types of Changes for CBE-30 Supplements

1.) Any change in process and/or process parameters

Examples:

- changes in concentration of reactants, reaction times, reaction temperatures and pressures
- changes in the order of addition of reactants
- changes in reaction pH
- changes in final distillation temperatures (e.g., water content of anhydrous steps)

Types of Changes for CBE-30 Supplements

2.) A change in the container closure system that does not affect the quality of the drug product

Examples:

- changes in the size or shape of a container for a sterile drug substance (The new container having the same quality glass, septum and crimp.)

Types of Changes for CBE-30 Supplements

3.) Relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA regulatory requirements

Examples:

- relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing
  (e.g., increasing the melting point range for mannose triflate, deleting the appearance acceptance criteria for mannose triflate or K222)
- making a change to an analytical procedure used for testing raw materials or drug substance intermediates that does not provide the same or increased quality assurance as the analytical procedure described in the approved application

Types of Changes for CBE-30 Supplements

4.) Addition of new PET manufacturing sites

- Additional facilities are required to be shown to operate identical to currently approved sites.
- A product comparability protocol is required by the FDA to be submitted with the CBE-30 supplement for the addition of new sites

Types of Changes for CBE-30 Supplements

5.) Labeling changes

Examples:

- addition of an adverse event due to information reported to the applicant or Agency
- addition of a precaution arising out of a post-marketing study

Submission of CBE-0 Supplements

- For certain types of changes, the holder of an approved application may commence distribution of the drug product upon receipt by the agency of a supplement for the change (i.e., there is no waiting period)
- If, after reviewing a CBE-0 supplement, FDA disapproves the change, FDA may order the manufacturer to cease distribution of the drug product made using the change
- If FDA informs the applicant that any information is missing, the applicant must cease distributing the drug product made using the change until the supplement has been amended to provide the missing information

Types of Changes for CBE-0 Supplements

1.) Addition to a specification or changes in the methods or controls to provide increased assurance that the drug substance or drug product will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess

Examples:

- adding a new test and associated analytical procedure and acceptance criterion
- improving an HPLC or GC method to increase the peak resolution
- increase the frequency of ClDG impurity testing

Types of Changes for CBE-0 Supplements

2.) Changes in the labeling to reflect newly acquired information to accomplish any of the following:

- to add or strengthen a contraindication, warning, precaution, or adverse reaction
- to add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product
- to delete false, misleading, or unsupported indications for use or claims for effectiveness

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- Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a **minimal** potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product do not need to be reported to the FDA immediately, but can be reported in the submission of the next scheduled Annual Report

Types of changes reported in Annual Reports

1.) Any change made to comply with a change to an official compendium that is consistent with FDA regulatory requirements

Example:

- change of USP ClDG specification from 1.0 mg/dose to 0.125 mg/mL

Types of changes reported in Annual Reports

2.) Replacement of equipment with that of the same design and operating principles

Example:

- replace Agilent GC with a Bruker GC using the same column and detector

Types of changes reported in Annual Reports

3.) The addition or revision of an alternative analytical procedure that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application

Example:

- add PTS as an alternative to the gel-clot test for BET

Types of changes reported in Annual Reports

4.) Tightening of acceptance criteria

Examples:

- reduce acceptance criteria concentrations for acetonitrile, K222 and BET
- increase radiochemical purity criteria

Types of changes reported in Annual Reports

5.) A change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied, that does not involve a change in the dosage strength

Examples:

- changes in the layout of the package or container label that are consistent with FDA regulations without a change in the content of the labeling
- editorial changes, such as adding a distributor's name
- labeling changes made to comply with an official compendium

Comparability Protocols

- An applicant may submit one or more protocols describing tests, studies and acceptance criteria to be achieved to demonstrate the absence of an adverse effect for specified types of manufacturing changes
- A comparability protocol can be used to justify a reduced reporting category for the particular change
- Any such protocols, if not included in the approved application, or changes to an approved protocol, must be submitted as a Prior Approval Supplement

Summary

The answer to the following question is how you assess and justify the reporting category used:

> *What is the potential (risk) for the change to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as they may relate to the safety or effectiveness of the drug.*

Summary

If the answer is a substantial potential exists for the change to have an impact on SISPQ (Strength, Identity, Safety, Purity, Quality)

- *Prior Approval Required*

If the answer is a moderate potential exists for the change to have an impact on SISPQ

- *CBE 0 or CBE 30*

If the answer is a minor potential exists for the change to have an impact on SISPQ

- *Annual report*

References

- Guidance for Industry: Changes to an Approved NDA or ANDA U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), April 2004, CMC, Revision 1
- Guidance for Industry: CMC Post-approval Manufacturing Changes Reportable in Annual Reports (DRAFT), U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), June 2010, CMC
- Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products Guidance for Industry (DRAFT), U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2015, Pharmaceutical Quality/CMC

Thank You