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POST APPROVAL CHANGES IN GENERIC DRUG PRODUCTS AND MARKETED DRUG PRODUCTS ACCORDING TO USFDA: A REVIEW

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ABSTRACT

The post approval changes are the changes made to generic and marketed drug products that have received an approval and to provide the data to support a change which would be considered suitable and sufficient to allow a determination of the impact of the change on the quality of the approved products as it relates to safety, efficacy and effective use of the products. After the approval of NDA or ANDA, the applicant may make post approval changes, provided the changes are reported to the FDA under the appropriate categories. Section 506 A of the Federal Food, Drugs and Cosmetics act and 21 CFR 314.70 provide for three reporting categories of the post approval changes namely: major change, moderate change and minor change. There are many reasons for making changes to pharmaceutical products after the original regulatory approval is obtained. Company change control procedures should detail how changes are evaluated and implemented as well as how the change impacts stability and what data will be needed to support the change. The regulatory group will determine the strategy for submission based on a review of the technical assessment of the change and the appropriate regulatory guidance.

KEYWORDS: NDA, ANDA, Post Approval Changes, Regulatory Approval, Generic Drugs, Marketed Drugs.

INTRODUCTION

A post-approval change management describes specific changes that a company would like to implement during the lifecycle of the product and how these would be prepared and verified.

Such a stepwise approach is expected to lead to faster and more predictable implementation of changes post-approval, since the Marketing Authorization Holder will have obtained agreement from the Regulatory Authorities about the proposed strategy and tests to verify the effect of the change on product quality.

The objective of this study is to classify the changes made to generic and marketed drug products that have received an approval and to provide the data to support a change which would be considered sufficient to allow a determination of the impact of the change on the quality of the approved products as it relates to safety, efficacy and/or effective use of the products.

Back ground

This includes emphasis on applying a science based and risk-based approach to the generic and marketed drug products quality assessment of these products. The draft guidance fills an important void as the existing guidance for industry.Q11 Development and manufacturing of drug substance (2012) barely touches on post approval changes for immediate release solid oral dosage forms, scale up and post approval changes, CMC, in vitro and in vivo documentation is more general and is limited to solid oral dosage forms. The new guidance provides more specific information on demonstrating equivalence between the approved and the proposed drug substance and supports a risk based assessment to help guide the decision making process.

As such, the guidance documents were needed on the information to support quality changes to new drug products which apply a modernized, science-based, and risk-based approach to this area.

Guidance for implementation

The following criteria are meant to provide guidance with respect to the classification of a change. Specific change examples based on the application of these criteria are provided in this guidance. For assistance in classifying a change, sponsors are advised to contact USFDA.

Post approval changes – US

In US post approval changes are designated as Scale Up and Post Approval Changes (SUPAC), the changes or reporting categories are categorized into three level:

- **Level I:** Major Changes

- **Level II:** Moderate Changes
- **Level III:** Minor Changes
- **Type of Application to be submitted**

Types of changes	Rules	Type of application
Major changes	21 CFR 314.70(b)	Prior Approval Supplement
Moderate changes	21 CFR 314.70(c)(5)	Changes Being effected in 30 days
	21CFR 314.70(c)(6)	Changes Being effected
Minor changes	21 CFR 314.70(d)	Annual report/notification

Upon regulatory approval of a new drug product, an applicant may propose postapproval changes to the product for various reasons, such as continuous improvement, compliance with compendial standards, and new suppliers or manufacturers for different components of the drug product. To do so, an applicant must notify FDA about each postapproval change via supplement or annual report, and also assess its effects before distributing a drug product made with such a change. The majority of the post-approval changes received by FDA is chemistry, manufacturing, and control (CMC) changes that may affect the following aspects of drug substances and/or drug products: components and composition, manufacturing sites, manufacturing process, specifications, container closure system, labeling, and multiple related changes. An applicant needs to submit a postapproval change request in the form of a supplemental (abbreviated) new drug application (sNDA/sANDA, or supplement), or needs to describe the changes in an annual report. These post-approval CMC changes may directly or indirectly affect the drug product quality and safety, and thus need to be evaluated by FDA using a risk- and science-based approach.

Based on the potential risk to product identity, strength, quality, purity or potency, postapproval CMC changes can be divided into four reporting categories:

- **Prior Approval Supplement (PAS):—** to report major changes that have substantial potential to adversely affect the drug product. Major changes need regulatory approval prior to distributing the drug product made using the proposed changes.

- **Supplement Changes being effected in 30 Days (CBE 30):—** to report moderate changes that have moderate potential to adversely affect the drug product at least 30 days prior to distributing the drug product made using the proposed changes. If FDA informs the applicant about missing information within 30 days of receiving a CBE 30, product distribution must be delayed until the CBE 30 is satisfactorily amended.

- **Supplement-Changes Being Effected (CBE 0):—** to report certain moderate changes for which product distribution can occur when FDA receives the supplement. If found not approvable upon regulatory review, FDA may order the applicant to cease the distribution of the drug product made using the proposed changes.

- **Annual Report:—** to report minor changes that have minimal potential to adversely affect the drug product. An applicant must describe minor changes in its next annual report.

Generic drugs play an increasing role in the US-healthcare system, saving billions of dollars each year while providing equivalent therapeutic effects just as their brand name counterpart. For instance, nearly 80% of prescriptions were filled with generic drug products in 2011 with a projection of 87% in 2015. The cost savings of the generic program alone for 2011 was $192.8 billion. All stakeholders, therefore, are allocating more attention and resources to generic drugs, while paying particular attention to their overall quality and safety. As part of product lifecycle management, appropriate postapproval CMC changes are crucial for quality assurance and continuous improvement.

Herein results are provided from a recent data-mining survey focused on postapproval CMC changes to approved generic-drug products. The goal is to reemphasize the criticality of postapproval product quality management, to improve the supplement submission quality from applicants, and to share the concept that the approval of a generic-drug product is just the beginning of its lifecycle.

The reporting categories for the post approval changes are provided with respect to the following

1) Components and composition
2) Manufacturing sites
3) Manufacturing process
4) Specifications
5) Container closure system
6) Labeling
7) Miscellaneous changes
8) Multiple related changes

1) Components and composition

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes requiring a prior approval supplement, unless exempted by regulation or guidance.

The deletion or reduction of an ingredient intended to affect only the color of the drug product may be reported in an annual report.

2) Manufacturing sites

Example under reporting category of major change (Prior approval supplement)

A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by FDA for the type of operation that is being moved or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than two years

Example under reporting category of moderate change (supplement changes being effected in 30days)

A move to a different manufacturing site for the primary packaging of

1) Any drug product that is not otherwise listed as a major change and
2) modified-release solid oral dosage form drug products.

Example under reporting category of moderate change (supplement changes being effected)

Move to a different manufacturing site for the manufacture or processing of the final intermediate.

Example under reporting category Minor Changes (Annual Report)

A move to a different manufacturing site for secondary packaging.

3) Manufacturing process

Example under reporting category of major change (Prior approval supplement)

Changes that may affect the controlled (or modified) release, metering or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.

Example under reporting category of moderate change (supplement changes being effected in 30days)

For the drug substance, redefinition of an intermediate, excluding the final material, as the starting material.

Example under reporting category of moderate change (supplement changes being effected)

A change in methods or controls that provides 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.

Example under reporting category of minor Changes (Annual Report)

A minor change in an existing code imprint for a dosage form. For example, changing from a numeric to alphanumeric code.

4) Specifications

Example under reporting category of major change (Prior approval supplement)

Establishing a new regulatory analytical procedure including designation of an alternative analytical procedure as a regulatory procedure.

Example under reporting category of moderate change (supplement changes being effected in 30 days)

Relaxing an acceptance criterion or deleting a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements.

Example under reporting category of moderate change (supplement changes being effected)

An addition to a specification that provides 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. For example, adding a new test and associated analytical procedure and acceptance criterion.

Example under reporting category of minor Changes (Annual Report)

Tightening of acceptance criteria.

5) Container closure system

Summary of major, minor and moderate changes

Major changes	Moderate changes	Minor changes
For liquid and semisolid dosage forms, a change in polymeric materials (e.g., plastic, rubber) of primary packaging components.	A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams, milliliters) of a non sterile drug product in a unit-of-use container.	A change in the size and/or shape of a container for a non sterile solid dosage form.
Single unit dose container to a multiple dose container size and shape of a container.		A change in the number of units (e.g., tablets, capsules) or labeled amount (e.g., grams) of non sterile solid dosage form in a multiple-unit container.

6) Labeling

A. General considerations: A drug product labeling change includes changes in the package insert, package labeling, or container label. In accordance with § 314.70(a), an applicant must promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with paragraphs (b) or (c) of § 314.70. All labeling changes for ANDA drug products must be consistent with section 505(j) of the Act.

Summary of major, minor and moderate changes

Major changes	Moderate changes	Minor changes
Changes based on post marketing study results, including, labeling changes associated with new indications and usage.	Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.	Changes in the layout of the package or container label that are consistent with FDA regulations Editorial changes, such as adding a distributor's name.

7) Miscellaneous changes

Major changes	Minor changes	Moderate changes
Changes to an approved stability protocol. An extension of an expiration dating period based on data obtained under a new or revised stability testing protocol that has not been approved in the application. Changes to a drug product under an application that is subject to validity.	Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product	An extension of an expiration dating period based on full shelf life data on production batches obtained under a protocol approved in the application

8) Multiple related changes

For multiple related changes where the recommended reporting categories for the individual changes differ, CDER recommends that the submission be in accordance with the most restrictive of the categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the submission be in accordance with the reporting category for the individual changes.

AIM

The aim of this study explains about post approval changes of the drugs according to the USFDA.

- The main objective of the study is about filing the changes happened in the dosage forms after its approval and type of changes made for safety and efficacy of the drug.
- To get the knowledge on different applications for filing the changes which are going to be approved.
- To know the type of submissions required to file a change.
- To get a sound knowledge on process filing post approval changes.
- To know the submissions provided along with the changes made.

  To know the changes made for generic and marketed drugs and its filing for the supplemental changes

METHODOLOGY

Post approval changes for a marketed drug product

Marketed drug product

These drugs are also known as branded or innovator drugs invented by pharmaceutical companies to prevent them from being copied or reverse engineered by other companies.

1. Facility changes, scale Changes and Equipment changes

Even a single specification of change has the ability to alter the end result of the entire drug formulation. The changes in facility, scale or equipment, should be reported or informed to the health authority. It should be noted that while making these changes, adjustments done to process parameters should only be limited to those needed to accommodate new equipment. A detailed account of facility, scale and equipment changes are as follows:

1. Facility changes

Facility changes are the changes in location of site of manufacture of intermediates and unfinished and final drug substances for both the company owned and the contract

manufacturing facilities. The applicant or DMF holder is responsible for ensuring that any new facility is aligned with current good manufacturing practice (cGMP) regulations. Typical facility changes that must be reported are, but not limited to:

- Addition of a new contract manufacturing facility for an intermediate by the drug substance manufacturer or an existing contract manufacturer
- Addition or relocation of an in-house intermediate manufacturing facility to a different campus
- Transfer of new contract manufacturing facility for an intermediate by the drug substance manufacturer or an existing contract manufacturer
- The addition or relocation of an in-house intermediate manufacturing facility to a different campus
- Transfer of an additional manufacturing step to a facility already being used got the other manufacturing steps
- Change of facility for the final purification or final manipulation of the drug substance
- Addition of an alternative manufacturing facility for the drug substance

B. Scale changes

Scale changes are the changes pertaining to the batch size outside the validated scale for intermediates, and the finished/unfinished drug substance. The section is relevant to changes of scale that use equipment of the following characteristics.

- Same equipment as listed in the current master batch record (MBR)
- Equipment that differs only in capacity from the equipment listed in current MBR
- Equipment of same construction material, design and operating principle as equipment listed in the current MBR

C. Equipment changes

It is related to changes in equipment that is of a different construction material, design or operating principle than the equipment listed in current MBR. Changes in equipment at an existing manufacturing facility must be reported. In case the organization has a contract manufacturer, a quality agreement must be made between the parties to ensure that changes in equipment made at the contract manufacturer are reported to the master file holder. A change to new equipment with different construction material, design or operating principle has greatest potential to adversely affect the physical properties of the drug substance if this

changed equipment is used during or after the final step or after subsequent processing procedures such as,

- Isolating the drug substance
- Drying the drug substance
- Reducing the particle size of the drug substance

2. Specification changes

This section entails information about specification changes to raw materials such as reagents and solvents, intermediates, drug substances including unfinished drug substances and changes to controls for critical steps (e.g. tests for control of reaction events).

1. **Specification changes to raw materials and intermediates: Generally, specification changes can be categorized into:**

- Changes made to comply with compendial changes, including the following:
  - USP Monograph or other compendial monographs for a raw material availability
  - USP Monograph or other compendial monographs for a raw material status update

- Changes that provide greater assurance of quality:
  - Tightening acceptance criteria
  - Adding a new impurity control
  - Revising an existing analytical procedure with an improved procedure
  - Revising specifications associated exclusively with improved analytical procedures

Other specification changes

- Relaxing acceptance criteria
- Deleting a test
- Replacing an existing analytical procedure with a new procedure
- Revising specifications associated with changes in supplier/grade of reagents or solvents, including the use of recycled solvents

B. Specification changes to drug substances

These changes to drug substance or unfinished drug substance include additions, deletions, or changes to analytical procedures. The exact nature of specification changes are as follows.

- When USP monograph becomes available or is updated, the drug substance's specifications should be updated with the compendial standards as appropriate

- Appropriate justification must be provided whenever an existing test is deleted, or routine test is changed to a skip test

3. Manufacturing process changes

Changes to the manufacturing process at/after final solution step are considered to have high potential to adversely affect the impurity profile and physical properties of the drug substance. This section includes a range of such process-related changes.

1. Changes that do not involve the route of synthesis

- Changes in unit operations such as addition, deletion, change in the order, or repetition of an existing unit operation on a routine basis
- Addition or deletion of raw materials like reagents and solvents or ancillary materials like resins, processing aids etc.
- Changes in solvent composition (other than for an analytical procedure covered in specification changes)
- Changes to process parameters such as temperature, pH, reagent stoichiometry, time etc. that are not related to scale or equipment changes

B. Changes in the route of synthesis in one or more steps

In general, these changes are considered to have a moderate to high potential to adversely affect the impurity profile of the drug substance. The manufacturing process should be validated using the new route of synthesis. Impurity carryover studies and spike/purge studies should be conducted as appropriate. Control of mutagenic impurities in or expected to be in the final drug substance should be evaluated according to ICH M7

4. Starting material changes

Changes in the vendor of the starting material may have a potential to adversely affect a drug substance's impurity profile depending on the starting material and its proximity to the drug substance. Changes to the route of synthesis or manufacturing process of the starting material that result in changes to the starting material specification could have a higher level of risk. Good manufacturing practice as described in ICH Q7 apply to the changes in Active Pharmaceutical Ingredients.

5. Contained closure system changes

The instructions on what are considered as contained closure system changes and how to deal with them are provided in the industry guidance released by the FDA. Organizations making post-approvals changes are instructed to follow the provided link.

6. Multiple changes

Multiple changes are those changes that involve a combination of changes dealt so far.
For example: a change to a new source of drug material, which brings in a change in facility, and any number of changes in manufacturing process potentially including a different route of synthesis can be referred to as a multiple change.

With extensive information on the glossary, identification of the post-approval changes to drug substances, and how to report them, the guidance may seem complex to decode. Hence, the needed action for organizations is to consult a Regulatory Affairs expert to thoroughly discern the criteria for post-approval changes and to proceed cautiously towards compliance. Be informed. Be compliant.

Post approval changes in IR solid dosage forms

Changes		**Level**	**Dissolution requirements**
Composition	Total excipients changes≤5%	Level 1	Dissolution release requirements
	Total excipients changes ≤10%	Level 2	Dissolution profile similarity in multiple media, unless active pharmaceutical BCS 1+ drug product dissolve>85% in 0.1N HCL in 15min
	Total excipients changes>10%	Level 3	In vivo bioequivalence
Site	Within same facility	Level 1	Dissolution release requirements
	Within same campus	Level 2	Dissolution release requirements
	Different campus	Level 3	Dissolution profile similarity in field medium
Batch size	Up to 10x	Level 1	Dissolution release requirements
	Beyond 10x	Level 2	Dissolution profile similarity in field medium
Equipment	Automation of transfer to alternate equipment	Level 1	Dissolution release requirements
	Different design or operating principle	Level 2	Dissolution profile similarity in field medium
Batch size	Changes within field and validated ranges	Level 1	Dissolution release requirements
	Changes within field and validated ranges	Level 2	Dissolution profile similarity in field medium
	Major changes	Level 3	In vivo bioequivalence

Post approval changes for generic drugs

Post approval CMC changes submitted to the Office of Generic Drugs (OGD) between calendar years 2005 and 2012 were surveyed from FDA's internal database. Qualitative and quantitative analyses were conducted upon categorizing these changes based on their nature, risk, and regulatory designations. Here we define "nature" as what is proposed to be changed, "risk" as potential adverse impact of the proposed changes on product quality and safety, and "regulatory designations" as filing categories identified by FDA after regulatory review. In addition, review outcomes (e.g., commonly seen deficiencies, comments, and filing issues) from OGD were summarized to identify major issues and areas.

Here, the two terms "supplement" and "postapproval change" are not inter-changeable because a supplement may contain or propose more than one postapproval change. Considering such a fundamental difference, the number of supplements and number of postapproval changes discussed here are different.

Common issues

- This section briefly summarizes commonly seen issues observed during this survey and a daily review of postapproval CMC changes, and accordingly, FDA's expectations on how to improve supplement submission quality. Commonly seen issues include: Section(s) of the 2004 guidance not cited to justify reporting category
- Lack of risk assessment to determine proper reporting category
- Lack of scientific reasons and/or rationale to support proposed changes
- Lack of proper investigation for OOS results
- Use of OOS results to justify new specification
- Reliance on data to justify reporting category
- Introduction of future CMC changes without supporting information
- Additional changes not listed in the cover letter
- No inspection date for site changes
- Lack of conciseness/clarification
- Too much unnecessary information provided.

To improve submission quality and facilitate timely review of thousands of CMC changes yearly, it is recommended that applicants do the following:

- Properly assess risks of proposed changes against published guidance, quality-by-design

- (QbD) principles, and/or internal knowledge
- Choose reporting category based solely on the risk assessment
- Clearly identify all proposed changes with brief risk assessment in the cover letter
- Provide supporting information necessary and sufficient to justify proposed changes.

4. RESULTS AND DISCUSSIONS

For generic drug products

On average, OGD received more than 3500 supplements each year within the survey period, and the yearly number of supplements submitted to OGD stayed relatively constant. Figure 1 shows a distribution summary for these supplements based on reporting categories designated by FDA upon review. As shown, the number of CBEs and CBE 30s received per year remained similar at ~20% and ~65%, respectively. However, the number of high-risk changes (i.e., PAS) appeared to be on the rise and they currently constitute approximately 10% of all the incoming supplements.

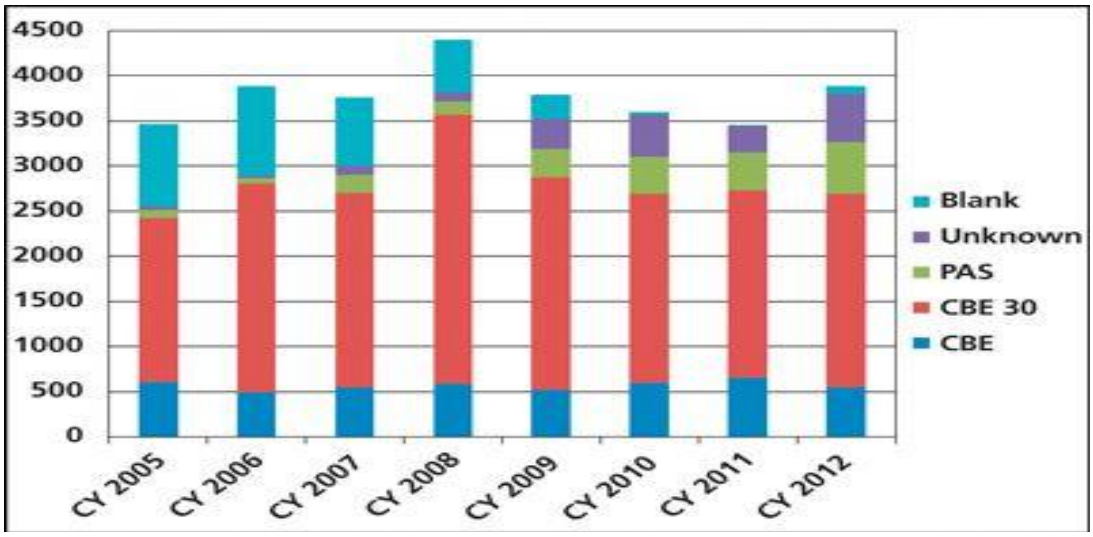

Figure 1: summary of supplements based on reporting categories from FDA (2005-2012).

Figure 2 summarizes commonly seen CMC changes, using data from calendar year 2012 to show a typical distribution of these changes. It is noticeable that three cohorts (i.e., facility, control, and manufacturing process) constitute nearly 85% of the proposed CMC changes in calendar year 2012. It provides further clarifications for these cohorts. Typically, postapproval changes in these cohorts are costly for applicants and resource consuming for both applicants and FDA, and may even delay product commercialization or lead to product recalls.

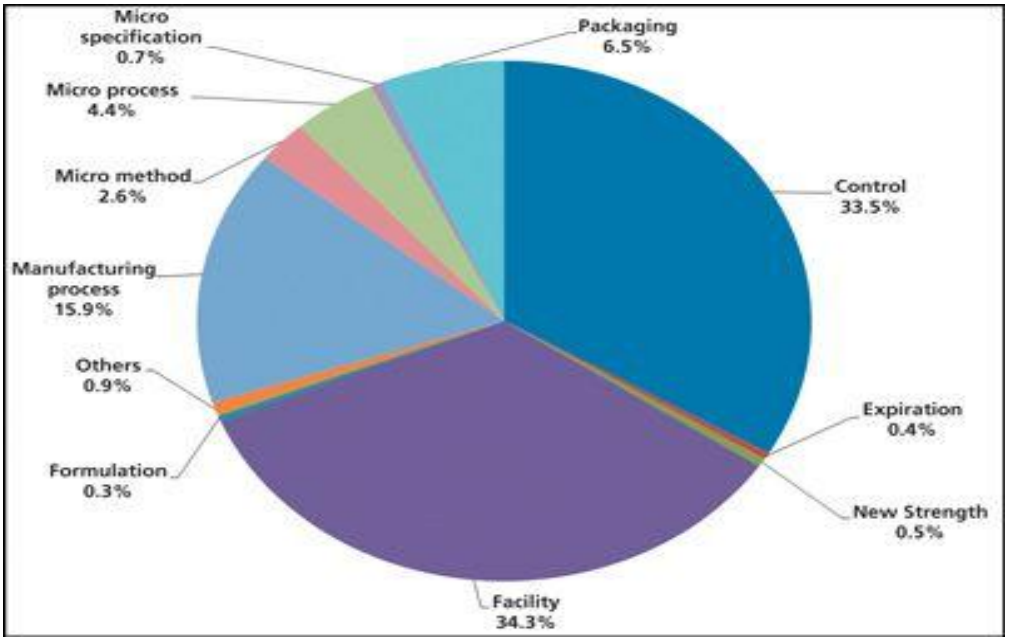

Figure: 2: commonly seen CMC changes.

PASs submitted in FY 2018 through FY 2022

Submission Type	Performance Goal
Standard PASs or PAS Major Amendments	90% reviewed within 6 months if preapproval inspection not required
	90% reviewed within 10 months if preapproval inspection required
Priority PASs or PAS Major Amendments	90% reviewed within 4 months if preapproval inspection not required
	90% reviewed within 8 months if preapproval inspection required and applicant submits a complete and accurate Pre-Submission Facility Correspondence (PFC) no later than 60 days prior to the date of the PAS or amendment submission, which remains unchanged
	90% reviewed within 10 months if preapproval inspection is required and applicant fails to submit a complete and accurate PFC no later than 60 days prior to the date of the PAS or amendment submission, or information in a complete and accurate submitted PFC changes
Standard and Priority PAS Minor Amendments	90% reviewed within 3 months of submission date

CONCLUSION

Knowledge of these differences will enable the sponsor of NDA, ANDA to develop the CMC strategy to implement change successfully in US. it provides detailed analysis of the current US regulations and guidance documents for post approval change management in marketed drugs and generic drugs. It also provides information regarding the submissions to be submitted for filing a change for its approval. it also provides an analysis of the approaches

described FDA draft guidance and post approval change management of CMC changes generic drug products and marketed drug products.

FDA receives more than 3500 supplements to marketed generic drugs each year. Proposed postapproval CMC changes directly impact product quality and performance, and eventually patient safety. Given the increasing importance of generic drugs in the US pharmaceutical supply chain, FDA is allocating more resources to ensure the timely evaluation of these postapproval changes. It is also applicants' responsibility to improve submission quality according to risk- and science-based principles, and to enhance lifecycle management of generic drugs using proper quality metrics (e.g., process capability). The authors believe that the findings presented here can provide valuable reference for the generic industry to submit high quality supplements, and for FDA to more efficiently manage and review them.

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