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Post Approval Regulatory Requirements for A New Drug Application (NDA)

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ABSTRACT

The objective of this paper is to give insight and better understanding of the regulatory requirements for changes done for an approved New Drug Application (NDA) in United States (US). For technical advancements, there may be situations which demand/ necessitate modifications for an approved NDA. The changes must be in conformance with the regulatory requirements of the Food and Drug Administration (FDA), the ultimate authority for the Drug related approvals in US. The changes must be systematically reported to the regulatory authorities in the recommended formats, termed as “Post approval changes for an NDA”. Section 506A of Federal Food, Drug, and Cosmetic Act, provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes. The FDA has revised its regulations on supplements and other changes to an approved application (21 CFR 314.70) to conform to section 506A of the Act. The changes can be major, moderate or minor depending on the changes likely to affect the quality, safety and efficacy of the product. Irrespective of the category of the changes, every change is to be brought to the notice of the US FDA in stringent, structured and stipulated format that are recommended for the regulatory advancements. If manufacturers are to achieve the much-heralded desired state, it is essential to allow some manufacturing changes. Firms would still be responsible for ensuring product quality. The goal is well known, the components needing change are well understood and characterized and the process well defined.

Key words: NDA, USFDA, Post approval changes, Regulatory Authorities

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INTRODUCTION

The New Drug Application (NDA) is the vehicle through which the drug sponsors formally propose the Food and Drug Administration (FDA) for approving the marketing of new pharmaceuticals in the United States (US)¹. NDA provides the complete information regarding the quality, safety, efficacy and other characteristics of the product. Changes are inevitable at times for an approved NDA, but reporting the changes are mandatory and are to be in compliance with the regulatory requirements of FDA. This article details the regulatory requirements and the ways of reporting post approval changes of an NDA to the FDA.

MATERIALS AND METHOD

The post approval changes are to be in accordance with section 506A of the Federal Food, Drug, and Cosmetic Act (the Act) and § 314.70 (21 CFR 314.70). The post approval changes are categorically reported as²

- Major changes
- Moderate changes
- Minor changes

1. Major change

A major change is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a Supplement and approval by FDA prior to distribution of the drug product made using the change.

This type of supplement is called, and should be clearly labelled, a “*Prior Approval Supplement*”. An applicant may ask FDA to expedite its review of a prior approval supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in it would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labelled, a “*Prior Approval Supplement - Expedited Review Requested*”. FDA is most likely to grant requests for expedited review based on extraordinary hardship for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

2. Moderate change

A moderate change is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.

There are two types of moderate change. One type of Moderate change requires the submission of a supplement to FDA at least 30 days before the distribution of the drug product made using the change. This type of supplement is called, and should be clearly labelled, a “*Supplement - Changes Being Effected in 30 Days*”. The drug product made using a moderate change cannot be distributed if FDA informs the applicant within 30 days of receipt of the supplement that a prior approval supplement is required. For each change, the supplement must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change. If FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the Supplement has been amended to provide the missing information. FDA may identify certain moderate changes for which distribution can occur when FDA receives the supplement. This type of supplement is called, and should be clearly labelled, a “*Supplement - Changes Being Effected*”. If, after review, FDA disapproves changes-being effected-in-30-days supplement or changes-being-effected supplement.

3. Minor change

A minor change is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next *Annual Report*.

Under § 314.70(e), an applicant can submit one or more protocols (i.e., comparability protocols) describing tests, studies, and acceptance criteria to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol that was not approved as part of the original application must be submitted as a prior approval supplement³.

GENERAL PRE-REQUISITES

Excluding editorial changes in priorly submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify FDA about each Change in each condition established in an approved application beyond the variations already Provided for in the application.

A supplement or annual report must include a list of all changes contained in the supplement or Annual report. On the list, FDA recommends that the applicant describe each change in enough detail to allow FDA to quickly determine whether the appropriate reporting category has been used. For supplements, this list must be provided in the cover letter.

In annual reports, the list should be included in the summary section. The applicant must describe each change fully in the supplement or annual report.

Table 1: Summary Types of Post-Approval Changes and Their Implications on the product⁴

	Major	Moderate	Minor
Definition	Change that drastically alters the efficacy and safety profile of the drug.	Change that moderately modify the safety and efficacy of the drug.	Change that slightly modify the efficacy and safety of the drug but almost harmless.
Approval status	Prior approval of FDA required to implement the change	FDA is informed about the changes, needs approval within 30 days	No need of any prior approvals for the changes intended
Release and distribution of drug product	Approval by FDA prior to distribution of the drug product made using the change is mandatory.	Unless the FDA disapproves, otherwise drug product can be distributed after 30 days	The drug product can be distributed, but the changes are to be clearly mentioned in the annual report
Documentation	Needs prior approval supplement and changes done to be notified in the annual report	Need Supplement - Changes Being Effected in 30 Days and Supplement - Changes Being Effected	Documented in the product annual report

Valuating the Effect of Manufacturing Changes

a. Assessment of the effects of the change

The approved application holder under section 505 of the Act must measure the effects of the change before distributing a drug product made with a manufacturing change. For each change, the supplement or annual report must contain information determined by FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change. This type of information must be included in supplemental application or in an annual report.

1. Conformance to specifications

An assessment of the effects of a change on the identity, strength, quality, purity, and potency of the drug product should include a determination that the drug substance, intermediates, in-process materials, and or drug product affected by the change conform to the approved specifications. A specification is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an Approved application to confirm the quality of drug substances, drug products, Acceptance criteria are numerical limits, ranges, or other criteria for the tests described (§ 314.3(b)). Conformance to a specification means that the specification, will meet the listed acceptance criteria.

2. Additional testing

In addition to confirming that the material affected by manufacturing changes continues to meet its specification, it is recommended that the applicant perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product have been or will be affected.

The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, and/or stability profiles. This additional assessment could involve testing of the post change drug product itself or, if appropriate, the material directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance and/or drug product, and the effect of the change on the quality of the drug product.

For an Instance: Evaluation of the hardness or friability of a tablet after certain changes.

b. Equivalence

On testing, the applicant should usually assess the extent to which the manufacturing change has impact on the identity, strength, quality, purity, and potency of the drug product. Usually, this is accomplished by comparing test results from before and Post change material and determining if the test results are equivalent.

c. Adverse effect

Some changes can adversely impact the drug product. In most of the cases, the applicant may not implement these manufacturing changes, but sometimes to do so. If an assessment indicates that a change has adversely affected the drug product, FDA recommends that the change be submitted in a prior approval supplement regardless of the recommended reporting category for the change.

For example, a process change recommended for a changes-being-effected-in-30-days supplement could cause the formation of a new degradant that requires qualification or identification. The applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant.

Nevertheless, it is recommended by FDA that the applicant should submit the respective change in a "Prior approval supplement" with appropriate information that supports the continued safety and efficacy of the drug product. During the review of the prior approval supplement, the FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product. The post approval changes are classified as per the category they belong to and the class of change.

Table 2: Classes of Post Approval changes and Categories they are Reported in^{5, 6, 7}

Categories of changes	Major	Moderate	Minor
Components & composition	Changes in the qualitative or quantitative formulation	Changes in components and composition	Changes in the color.
Manufacturing process	Replacing a Class 100 aseptic fill area with a barrier system or isolator for aseptic filling.	An increase or decrease in production scale during finishing steps that involves different equipment	A minor change in an existing code imprinted for a dosage form. For example: changing from a numeric to alpha-numeric code.
Specifications	Deleting any part of a specification except as otherwise provided for in the guidance.	Any change in a regulatory analytical procedure other than those identified as major changes or editorial changes.	Tightening of acceptance criteria.
Manufacturing sites	A move to a different manufacturing site, one used to manufacture or Process a drug substance when the new manufacturing site does not have a cGMP inspection for the type of operation.	A move to a different manufacturing site for the manufacture or processing of the final intermediate.	A move to a different manufacturing site for secondary packaging.
Container closure system	A change in the primary packaging components for any drug product when The primary packaging components control the dose delivered to the Patient	A change in or addition or deletion of a desiccant.	Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap.
Labeling⁸	Changes based on post marketing study results, including, but not limited to, labeling changes associated with new indications and usage.	Addition of a precaution arising out of a post marketing study.	Labeling changes made to comply with an official compendium.
Miscellaneous Changes	Addition of a stability protocol or comparability protocol.	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.

In addition to reporting the changes made, an applicant making a change to an approved NDA under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (cGMP) requirements of the Act (21 U.S.C. 351(a) (2) (B)) and applicable regulations in Title 21 of the Code of Federal Regulations. Further, the applicant should also consider all relevant CDER guidance documents for recommendations on the information that should be submitted to support a given change.⁹

CONCLUSION

Changes are inevitable in pharmaceutical industry in fact they are very much necessary for the continuous Quality improvement of the product. By a thorough understanding of the relevant regulatory requirements stated in the act and the related guidance documents, the applicant can plan the necessary changes to the approved NDA. The applicant should think back the impact of the change on the Quality attributes of the final product and should report the changes for an approved NDA for regulatory authorities in a timely manner^{10, 11} to be in compliance with FDA. This ultimately benefits the manufacturers in preventing the 483's and warning letters from the FDA and also can give the best possible quality Medicines that would be compliant both for patients and FDA as well.

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