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POST APPROVAL ANNUAL REPORTABLE MANUFACTURING CHANGES IN US

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Abstract

A large number of Chemistry, Manufacturing and Control (CMC) changes are being submitted to US FDA every year .These changes may be Major changes which are submitted as Prior Approval Supplement (PAS) , Moderate changes which will be submitted as Changes being effective in thirty days (CBE-30) and Minor Changes such asChanges being effective on same day (CBE-0) and changes only notified in Annual Report.There are some changes which are likely to have minimal potential to cause adverse effect on Product quality,efficacy and safety.This article will discuss the manufacturing changes which will fall under the category of Annual Reportable changes and documents required to file these changes.[1]

Key words: Annual Reportable, US FDA, CMC, Minor Changes and Stability data

Introduction

Food and Drug Administration Modernization Act was signed by US President on November 21, 1997. The Modernization Act was amended by adding section 506A, which provided requirements for reporting manufacturing changesmadeto an approved application.The FDA approval is required to distribute the product which has been manufactured with proposed changes.As a result of introduction of the Modernization Act, the FDA revised its regulations for filing supplements and other changes to an approved application (21 CFR 314.70).The US Food and Drug Administration (FDA) has published guidance on post-approval changes which clearly mentions the changes which are to be reported in annual report by manufacturer or application holder of new and generic drug products.[2]

Generally, there are three ways of reporting the changes to New Drug Application or Abbreviated New Drug Application (ANDA):

- Major Change-Prior Approval Supplement (PAS)
- Moderate Change-CBE-30
- Minor Change-CBE-0 & Annual Report

MajorChange:

The changes which are made by manufacturer to existing product and having potential to effect quality, safety and efficacy of the product are called major changes. These changes need to be notified to FDA prior to implementation as PAS. Some important examples of changes which fall under this category of are listed below:

- Introduction of new-strength of existing drug product
- Change in the basic manufacturing step e.g. Dry to wet granulation
- Change in the method of drug substance manufacturing which leads to change in impurity profile.
- Change in the ink code imprint or change in the ink used for solid dosage form
- Change in source of material for drug substance and drug product.
- Addition of new equipment in the line of manufacturing.
- Change in the method of sterilization.
- Change in the formulation of approved drug product.[3]

Moderate Change:

The changes which are having moderate potential to effect quality, safety and efficacy of the product are called moderate changes. These types of changes need to be notified to FDA prior to implementation as Changes Being Effective in 30 days (CBE-30). These changes can be implemented within 30 days of notification without approval on manufacturer's risk. Some important examples are listed below:

- Change in manufacturing site for drug product, drug substance and for in-process material.
- Change in primary packaging site
- Testing Facility for Drug substance, In process and Finished product.[3]

Minor Change:

The changes which are having minimal potential to effect quality, safety and efficacy of the product are called minor changes. These types of changes can be notified to FDA after implementation as CBE-0 i.e. the change being effective on the same day or only in annual report. However, summary of all types of supplement filed for A specific product in a year will be mentioned in an annual report for that particular product.

Some important examples are listed below:

- Change in manufacturing site used for secondary packaging
- Change in manufacturing site for Labeling
- Change in manufacturing procedure from Terminal Sterilization to Aseptic filing.
- Change in Order of addition of ingredients.
- Change in the shape and size of container for nonsterile products.
- Change in number of dosage units e.g. number of tablets in bulk pack or no of capsules in bulk pack.
- Change in Child Resistant Closure of a bulk pack.[3]

Discussion

In Today's Scenario the competition between pharmaceutical manufacturers is very high.Every manufacturer is keen to capture market by providing upgraded products. As a result, every single day so many applications for new inventions and modification in existing products are being filed. The manufacturers having registered products in US and intended to implement manufacturing changes, FDA has clearly mentioned in guidelines based on 21 CFR 314.70 that on the basis of circumstances manufacturer need to inform FDA in suitable format.

The category of changes which fall under **Annual Reportable Changes** are detailed below:

Components and Composition

- Updating of Batch Formula Record (BFR) for Overage reduction which is compensating the manufacturing loses.
- Change in Excipient Supplier with no change in approved specification.
  Removal of Coloring and flavoring agent which does not impact quality and Impurity profile.[4]

Manufacturing Sites

- Minor structural changes made to the sterile product manufacturing facility which do not affect the quality of the product.
- Addition of barriers in filling area to avoid human interventions.
- Change in Contract Manufacturing Organization used for washing and drying of stoppers with certification that there is no impact on quality of washing and drying.[5]

Specifications

- Addition of new tests in approved specification.
- Tightening of Impurity Limit.
- Compliance of Specification to official compendia without relaxing of limits
- Replacement of test with an equivalent test.
- Increase in test of packaging material to enhance the quality[5]

Manufacturing Process

- Change in mixing time in Blending step
- Change in drying time for Immediate release dosage forms
- Addition of new step in manufacturing of Drug producte.g. addition of sieving To remove aggregates[5,6]

Manufacturing Equipment

- Replacement of equipment having same working capacity, design and operating principle and no change in In-Process parameters.[7]

Manufacturing Batch Size

- Modification in Batch scale such that it results from combining previously separated batches of in-process material to perform the next step in the manufacturing process[8]

Container Closure system

- Modification in the container/closure system for the storage of a nonsterile drug substance so that no change in extractable profile.
- Change in desiccant so that the new desiccant is already being used in a approved product.
- A change in glass supplier being used for packaging of drug product without a change in glass type.
- Change in ferrule and flip cap or Overseal of cap without change in the color of cap and no change in the Container Closure Integrity.

Labeling Changes

- Reflection of the Revision in drug product Labeling which have been already submitted in CBE-0 with updated Structured Product Labeling. Also mentioning effective and safe use of drug.[6]

Details of eCTDsections containing Annual Report Information which are to be submitted toUSFDA are provided below:[9]

Sections	Subsection	Name of document
1.1 Forms		
	1.1.2	Form 356h
	1.1.3	Form 3397
	1.1.4	Form 2252
1.2 Cover letters		
1.3 Administrative information		
	1.3.2	Field copy certification
	1.3.3	Debarment certification
	1.3.5	**Patent and exclusivity**
	1.3.5.1	Patent information
	1.3.5.2	Patent certification
	1.3.5.3	Exclusivity request
1.4 References		
	1.4.1	Letter of authorization
1.13 Annual report		
	1.13.1	Summary for nonclinical studies
	1.13.2	Summary of clinical pharmacology information
	1.13.3	Summary of safety information
	1.13.4	Summary of Labeling changes
	1.13.5	Summary of manufacturing changes
	1.13.6	Summary of microbiological changes
	1.13.7	Summary of other significant new information

	1.13.11	Distribution data
	1.13.12	Status of post marketing study commitments
	1.13.13	Status of other post marketing studies
1.14 Labeling		
	1.14.1	**Draft Labeling**
	1.14.1.1	Draft carton and container labels
	1.14.1.2	Annotated draft Labeling text
	1.14.1.3	Draft Labeling text
1.14.2 Final Labeling		
	1.14.2.1	Final carton or container labels
	1.14.2.2	Final package inserts (package inserts, patient information, Medication guides)
1.14.3 Listed Drug Labeling		
	1.14.3.1	Annotated comparison with listed drug
	1.14.3.2	Approved Labeling text for listed drug

Case Study

A Generic Drug Manufacturer proposes A minor correction in Packaging Insert, Addition of new test in specification, Addition of new Drug Product manufacturing site and change in primary packaging site. The supplement to be filed by the manufacturer and sections of ANDA application affected or need to be revised to implement the change are listed below:

Proposed Change	Category Type	Revised Documents	Inclusion in Annual Report
Minor correction in PI*	CBE-0	Package Insert	Yes
Addition of new test in specification**	Annual Report	Specification and Test Procedure	Yes
Addition of new DP[#]manufacturing site	PAS	All documents submitted at the time of ANDA submission.	Yes
Change in primary packaging site	CBE-30	The documents where the name of packaging site will appear.	Yes

*Package Insert
**Additional test included only for quality assurance not to justify a failed test.
[#]Drug Product.

Importance of Categorically Listing of Manufacturing Changes

- FDA has published all relevant information in guidelines and in CFR 314.81. Therefore, lot of information is available under one umbrella for reference of ANDA holder.
- ANDA holder can easily evaluate on the basis of category provided in guidelines and can decide the type of supplement he need to submit to implement the change.
- The documents can be revised accordingly.
- Reviewer can easily evaluate the supplement application submitted for approval of change as per checklist mentioned in guidelines.
- FDA keep on updating the information and requirements as per query received and observations in other cases which are available for reference to all.

Conclusion

The Annual Report guidance provided by FDA continuously reminds a pharmaceutical organization that A change in manufacturing facility not only to be reported, must be implemented with compliance of cGMP requirements. Annual reports support in making product manufacturing records easily traceable by the members of organization as well as to the auditor. It benefits in avoiding confusion at the time of commercialization. Production unit can easily refer current approved documents and without wasting time batches can be planned.

Therefore, all pharmaceutical organizations are suggested to submit Annual reports with current Qualifying Equipment, Validated Test Procedures, scientifically established commercial manufacturing process and stability studies depending on the nature of the change

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