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POST APPROVAL STABILITY STUDIES AND PROTOCOLS: AN OVERVIEW

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ABSTRACT

The objective of stability study is to determine the shelf life of drug/drug product in which the drug/drug product still meets its established specifications and to ensure the suitability of packaging material and conditions of storage. The preformulation stability studies were started during early phase of development in between preclinical and clinical study. During the clinical studies parallel stability studies of drug product has to be conducted to file the NDA as per ICH Q1A (R2) guidelines. After getting NDA approval there is requirement of post approval stability data to ensure the validity of previously determined shelf life of the drug product and if there is any change the process/excipients etc. The United States Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA) provide guidelines on additional stability studies for post-approval changes in site, scale, manufacturing and process for dosage forms.

Keywords: ***FDA, ICH, OOS, OOT and post approval***

Introduction:

This article presents an overview of post approval stability studies after approval of the FDA of the drug substance and drug product to routine manufacture and marketing. Proper design, implementation, monitoring and evaluation are crucial for obtaining useful and accurate stability data. Stability studies are linked to the establishment and assurance of safety, quality and efficacy of the drug product from early phase development through the lifecycle of the drug product [1, 2, and 3]. From post approval stability study one have to ensure the validity of optimal storage and packaging conditions and confirm the shelf life of same product (follow up study) or after any change in manufacturing process,

primary packaging and change in excipients etc.

Post Approval (Marketing Phase):

To ensure the stability of marketed product and manufacturer's claim on stability and shelf life of the product one have to perform stability check after getting the approval where manufacturer already submitted the at least 6 month stability data as per the ICH QA (R2) guideline and stability zone [1, 4, 5, 6] . During post approval stability one has to consider the following points:

- At least one lot of drug substance and one lot of each packaging type for drug product produced each year should be placed on long term stability.
- Additional stability testing may be required to support process changes for drug substances and/ or drug product.
- The filing requirement for changes are covered in multiple FDA guidance documents addressing drug product changes (SUPAC- scale up and post approval changes) and drug substance changes (BACPAC- bulk active post approval changes).

Post approval studies include:

1.Studies for changes/ variations

Confirmation of shelf life and storage condition (quality) after changes in-

- Manufacturing process
- Primary packaging
- Change in excipients
- Change in drug substance

Data required for submission includes minimum 6 months data / 3 batches worst case testing-

- Storage under relevant climatic condition.
- Only the sample stored under stricter condition is analysed (thus covers the lower condition).
- In case of OOS (out of specification) results the sample stored under lower condition will be analyzed too.

Protocols for post approval stability studied for changes/ variations:

i.Stability setup for product stable at room temperature(Post approval protocol):

Storage Conditions	Months								
	3	6	9	12	18	24	36	48	60
25ºC / 60 % RH	a	a	a	a	a	a	a	a	a
30ºC / 75 % RH	x	x	x	x	x	x	x	x	x
40ºC / 60 % RH	x	x							

x = analysis, a = analysis, if 30ºC / 75 % RH is OOS

Table I: Protocol for post approval stability study for product stable at room temperature

ii.Stability setup for products intended for storage in a refrigerator (Post approval protocol):

Storage Conditions	Months								
	3	6	9	12	18	24	36	48	60
-20ºC									a
5ºC	x	x	x	x	x	x	x	x	x
25ºC / 60 % RH	x	x							

x = analysis, a = reference

Table II: Protocol for post approval stability study for product intended for storage in a refrigerator

The samples can be placed at 5ºC for long term study with a sample at -20ºC analyzed at the end of study. The normal room temperature (25ºC / 60%RH) is accelerated condition and sample placed can be analyzed after 0, 3 and 6 months to compute the final result.

iii.Stability setup for products intended for storage in a freezer (Post approval protocol):

Storage Conditions	Months								
	3	6	9	12	18	24	36	48	60
-20ºC	x	x	x	x	x	x	x	x	x
5ºC	x	x							

x = analysis, a = reference

Table III: Protocol for post approval stability study for products intended for storage in a freezer

The samples were placed at -20ºC for long term study and were analyzed regularly at proposed retest period. The samples put at 5ºC were analyzed at 0, 3 and 6 months (at least 3 times point) to compute the final result and to ensure the stability of product post approval.

Follow up stability studies (ongoing stability)

In follow up stability studies one have to confirm the validity of shelf life and storage condition (quality) for marketed products.

Selection of batches:

Every year one commercial batch of each product formulation, in each formulation strength, in each packaging configuration is subjected to follow up stability programme.

Storage condition

Samples are stored accordingly to their validity and storage remark. (5°C, 25°C / 60% RH and for 30°C / 75% RH). Samples are

stored in representative packaging configuration.

Test Frequency (follow up study)

- Testing should be minimum, after 1 year and end of shelf life.
- For US market products – 4 sampling time point or annually.
- According to NDA-Test frequency might be increased by QA for critical products.

Worst Case Testing

- Store the samples under relevant climatic condition.
- Only the samples stored under stricter condition is analyzed.
- In case of OOS (out of specification) the samples stored under lower condition is analyzed.

Protocols for post approval follow up stability studied:

i.Stability setup for product stable at room temperature with a storage remark "Do not store above 30ºC" (Post Approval Follow Up Stability Protocol):

Storage Conditions	Sampling Point	
	12 months	End of Shelf Life
25ºC / 60% RH	a	a
30ºC / 75% RH	x	x

x = analysis, a = analysis, if 30ºC / 75 % RH is OOS

Table IV: Protocol for post approval follow up stability study for products stable at room temperature with a storage remark "Do not store above 30ºC"

ii.Stability setup for products stable at room temperature with storage remark "Do not store above 25ºC" (Post Approval Follow Up Stability Protocol):

Storage Conditions	Sampling Point	
	12 months	End of Shelf Life
25ºC / 60% RH	x	x

x = analysis

Table V: Protocol for post approval follow up stability study for products stable at room temperature with storage remark "Do not store above 25ºC"

iii.Stability setup for products intended for storage in a refrigerator (Post Approval Follow Up Stability Protocol):

Storage Conditions	Sampling Point	
	12 months	End of Shelf Life
5ºC	x	x

x = analysis Table VI: Protocol for post approval follow up stability study for products intended for storage in a refrigerator

Post Approval Stability Data

Stability issue management [7, 8, 9, 10]:

OOS: Out of Specification

If analytical value was found outside of the registered specification at any time point, the product is said to be out of specification (Figure I).

OOT: Out of Trend

If analytical value was found outside experience but within the specification (no OOS) then the product is said to be out of trend.

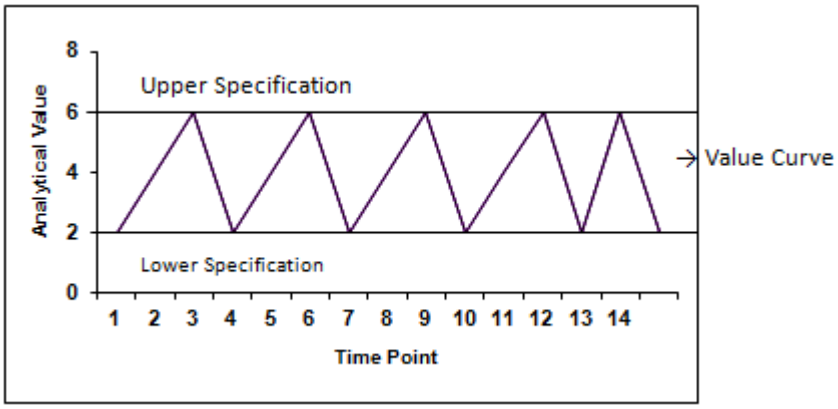

Figure I: Quality Control Chart with Upper and Lower Specification

The following points should be considered during computing the final conclusion regarding the stability:

- If there is any OOS analytical value found in the study, we have to evaluate the analytical procedure weather it is stability indicating and ensure the analytical procedure is validated.
- If we found no issue with stability indicating analytical procedure then this issue is more complex and product on the market could be affected.
- This may lead to a recall of the product from the market after checking whether the study is relevant for the marketed product and weather the shelf life or storage remark are affected and which country are affected most based on stability data and mean kinetic temperature.
- Further decision is made to change of validity (re-adjustment of shelf life), improvement if OOS does not affect efficacy and safety of product otherwise we have to recall the product from the market.

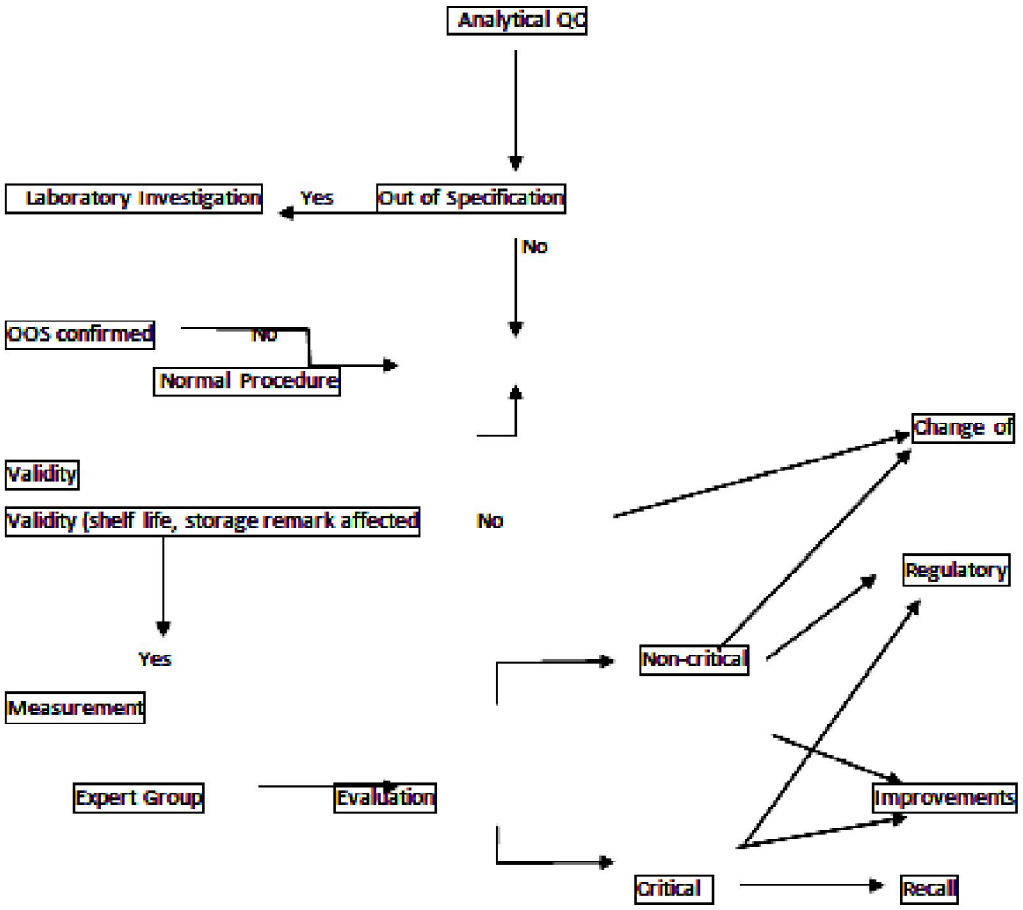

Figure 2: Decision Tree for Post Approval Stability Data

Conclusion:

Stability is interwoven through the entire fabric of the drug product lifecycle. This review presents an overview of post approval stability testing of drug products and provides a detailed understanding of the subject and protocols. Post approval stability has equal importance to stability studies done earlier before filling IND and NDA. After getting approval we have to validate the previous study claims in follow up post approval stability study and further ensure the equality of shelf life if any changes occur in drug/drug product after getting the FDA approval. A carefully designed protocol is required to minimize the product failure.

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