International Journal of Pharmaceutical and Life Sciences
ISSN 2305-0330
Volume 3, Issue 1: February 2022

THE RISK-BASED APPROACH IN CASE OF A MATERIAL CHANGE IN PHARMACEUTICAL OPERATIONS

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Abstract

Change of material source is very common in the pharmaceutical company. In general, the change of material triggers process validation. In this article, the need and extent of process validation have been discussed considering the risk-based approach. Risk assessment should be performed by comparison between old Vs new material, impact assessment due to material change, and material characterization where applicable. Based on risk assessment, it can be concluded that new material is 'comparable and usable' or 'not comparable but usable' or 'not comparable and not usable.' Accordingly, the need and extent for process validation and stability requirements can be concluded.

Keywords: Material Change, Risk-based approach, Process Validation, Pharmaceutical

Introduction

In general, process validation is required if the source of active pharmaceutical ingredients (API)/ excipients of the pharmaceutical product is changed. Such change is evaluated through a change control procedure with the support of risk assessment.

WHO guideline[1] on non-sterile process validation says, "…..Validation should be considered when changes to production and/or control procedures are planned. Based on risk assessment, changes that may require revalidation could include (but are not limited to):
— changes in the master formula, methods, starting material manufacturer, starting material manufacturing process, excipient manufacturer, excipient manufacturing process…."

As per EU Guideline for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use[2]: "Written procedures should be in place to describe the actions to be taken if a planned change is proposed to a starting material, product component, process, equipment, premises, product range, method of production or testing, batch size, design space or any other change during the lifecycle that may affect product quality or reproducibility…..

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Currently, the author is working as Manager, Quality Assurance in Square Pharmaceuticals Ltd. Bangladesh. The concept described in this article is based on the author's opinion and experience and considering GMP guidelines on change management.

Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance, and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts."

US FDA guideline[3] says, "With a lifecycle approach to process validation that employs risk-based decision making throughout that lifecycle, the perception of criticality as a continuum rather than a binary state is more useful. All attributes and parameters should be evaluated in terms of their roles in the process and impact on the product or in-process material, and reevaluated as new information becomes available. The degree of control over those attributes or parameters should be commensurate with their risk to the process and process output."

As per ICH guideline[4], "A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk-based assessments."

Above mentioned GMP guidelines instruct to assess of any change through risk-based approach. In this article, the same approach has been applied in case of material change. If any local regulatory requirement is stricter, the local requirement should be implemented.

This article describes the process for evaluation and implementation of changes to Active Pharmaceutical Ingredients (API), excipients, and packaging materials used for Drug Product (DP) manufacture in compliance with regulatory guidelines.

Reason for Change of Materials

Changes in materials can be due to various reason(s). Following are some examples:

- Change of the manufacturing site of supplied material, intermediate and /or starting material
- Changes on the manufacturing or packaging process or equipment or starting materials
- or change of material specification
- or combination of above in different orders
- or use of alternate material or grade of material

Evaluation Process of Material Change

Evaluation process will include following steps:

- Comparison and impact assessment (on material)
- Additional characterization and review
- Risk assessment (for Drug Product and Finished Dosage Form) and conclusion
- Implementation strategy

Effort for evaluation should be commensurate with general risk of change (for example: risk presented due to change in API is generally much higher than risk presented due to change of GMP consumable and hence efforts required for evaluation and implementation of API changes are much higher).

Comparison and Impact Assessment

Following steps should be followed for comparison and impact assessment:

a. Comparison of currently used material Vs proposed material

Comparison of currently used material and proposed material with change based on information (comparison attributes are linked to risk posed by the item and change and can be reduced for excipients, and packaging material based on rationale):

- Comparison of manufacturing flow chart for manufacturing process and inputs
  - ✓ Material changes (changes to intermediate or starting material or additives)
  - ✓ Equipment changes (changes to process equipment including batch size changes and site changes)
  - ✓ Manufacturing process changes (e.g. critical process parameters changes)
- Comparison of specifications of currently used material and proposed material
- Comparison of stability data from vendor (if any)
- Comparison of functionality data from vendor (if any)
- Comparison of packaging (including changes to packaging materials, containers, use of desiccants or absorbers, etc.)
- Health Safety and Environment (HSE) related changes (if any)
- Any other changes (grade or pharmacopoeial designation or nomenclature, etc.)
- Vendor history for past material and reason for change

b. Comparison of actual material

At least, three lots of samples of material with change must be tested and compared with data of existing material.

Additional characterization and review

Based on material, critical material attributes for the material are selected. Appropriate characterization information is summarized. If characterization reveals differences that can impact functionality, process ability, purity, stability or failure to meet filed documentation then additional studies (characterization and or technical batches, etc.) may be required.

Risk assessment and conclusion

Based on above comparisons, a risk assessment should be performed to understand impact on drug product. Conclusion and recommendation for use should be defined.

Based on impact assessment and additional characterization, following conclusions are required to claim material is comparable:

- Old and new material are physico-chemically comparable (match of attributes)
- Change of material will not need change to any operational parameter or control strategy (reflection of process ability) or analytical procedures (as currently validated) and
- Critical quality attributes (impacted by functionality), hold times and the stability of product will not be adversely impacted

Based on impact assessment and additional characterization, following conclusions are required to claim material is useable:

- Old and new material are chemically same (same label composition and label claim)
- Change of material may need change to operational parameters and/or control strategy or analytical procedures (as currently validated) and
- Critical quality attributes and expected stability of product will not be adversely impacted

Results of characterization and comparison will lead to one of following scenarios:

- Material is comparable and usable
- Material is not comparable but usable
- Material is not comparable and not usable

Implementation strategy

Implementation strategy will consider risk assessment and conclusions including regulatory risk. In case where material is not comparable and not usable, change of material should not be performed.

API related changes

In case where material is comparable, usable and meet all following pre-requisites, change can be implemented without need for verification or validation batches as these conditions represent minimal risk:

- Change is an early manufacturing stage change in production of API
- There are no changes in solubility rate, impurity profile and stability profile of API (with no changes in physical characterization of material or no changes in catalyst (if any))
- API has high solubility, is rapid dissolving and there are no other associated formulation or process changes for formulation
- API polymorphs are well characterized (if polymorphs exist)
- No other formulation and process changes are associated with this change

In case where materials are comparable and usable, minimum one verification batch in commercial setting should be produced to demonstrate that the proposed combination of process parameters (as validated) and material attributes are capable of manufacturing acceptable quality product at commercial scale. Verification strategy can use matrixing or bracketing for different strengths for same formulation. Following scenarios are example scenarios:

- Change in late manufacturing stage of API (no impact on the physical characteristics including particle size distribution, particle shape, etc.)
- There are no changes in solubility rate of API, impurity profile and stability profile of API and
- No other formulation and process changes are associated with this change

In case where materials are not comparable but usable, validation strategy (including technical batches or additional characterization, if required) should be summarized. Validation strategy should use minimum three batches and provide documented evidence that the process, operated within established parameters, using material (post change) can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Matrixing or bracketing or family approaches can be used based on appropriate documented rationale.

Excipient and packaging material related changes

For material considered as comparable and usable, implementation strategy should be based on regulatory and quality assessments.

For material considered as not comparable but usable, implementation strategy should be based on regulatory, quality assessments and validation requirements where applicable.

Stability requirements

Stability requirements for API and excipients changes must follow decision based on table below at minimum. Additional stability studies due to stringent requirements (triggered due to regulatory requirements or risk assessment) take precedence.

Change Category		Implementation strategy	Stability data (6 months) from technical/pre-validation batches incorporating change available	Accelerated stability data (3 months) and stability data (6 months) from technical/pre-validation batches incorporating change available	Additional stability requirements for release of product to market
API Changes					
	Comparable and usable	Implement as is	-	-	First commercial batch subjected to real time stability (batch can be released initiating stability study)
	Comparable	Verification	Yes	-	No

Change Category		Implementation strategy	Stability data (6 months) from technical/pre-validation batches incorporating change available	Accelerated stability data (3 months) and stability data (6 months) from technical/pre-validation batches incorporating change available	Additional stability requirements for release of product to market
	and usable	batch	No	-	6 months real time stability data required (3 data points minimum)
	Not comparable and usable	Validation	-	Yes	3 months stability data from validation batches
			-	No	Accelerated stability data (3 months) and real time stability data (6 months)
Excipient/ Packaging material Changes					
	Comparable and usable	Verification Batch if applicable	-	-	Real time stability based on risk assessment (batch can be released initiating stability study)
	Not comparable and usable	Validation if applicable	Yes	-	Real time stability based on risk assessment (batch can be released initiating stability study)
			No	-	6 months stability data required (3 data points minimum)

Stability study conditions need to be defined based on supply markets and regulatory requirements.

Conclusion

Risk-based approach mentioned in this article can be applied to avoid unnecessary process validation in case of material change.

References

1. World Health Organization. (2015). Forty-ninth report of the WHO Expert Committee on specifications for pharmaceutical preparations. Annex 3- Guidelines on good manufacturing practices: validation, page 85
2. EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use- Annex 15: Qualification and Validation, page 13
3. US FDA, January 2011, Guidance for Industry, Process Validation: General Principles and Practices, page 7
4. ICH Harmonised Tripartite Guideline. (2008). Pharmaceutical Quality System Q10, page 10