

1 Purpose

The purpose of this guideline is to provide guidance regarding the reworking, reprocessing or recovery (salvaging) of formulated products, active pharmaceutical ingredients (API's) and intermediates used in the processing of APIs.

2 Scope and Applicability

This document is applicable to all commercial products manufactured within A manufacturing facility. Products used or manufactured within R&D facilities solely for R&D purposes are excluded. Local or national Regulations may take precedence over this guideline.

3 Definitions

3.1 Product

Formulated Product, API or API intermediate.

3.2 Re-treatment

Re-treatment is the general term applied to any recovery, rework or reprocess activity.

3.3 Re-processing

Reprocessing is the act of repeating process step(s) that is (are) part of the established manufacturing process for product.

Note:

For formulated product reprocessing is carried out on product of unacceptable quality so that its quality may be rendered acceptable. For APIs and intermediates reprocessing can also be carried out on product that meets established specifications e.g. in order to combine smaller amounts.

3.4 Reworking

Reworking is subjecting all or part of a batch of product that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain an acceptable quality product.

3.5 Recovery

Recovery is the introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

Note:

For APIs and intermediates the isolation (recovery) from previous batches may

performed.

Out of Specification batches must not be blended for the purpose of meeting specification.

Where blending is carried out blended batches must be traceable back to individual batches and the blend must be tested for conformance to specification and have expiry or retest life based on the oldest material used in the blend.

5.2 Suitability for Retreatment

Before a decision is taken to retreat a product its feasibility should be technically assessed and the assessment approved by Quality Assurance. In addition Quality Assurance should also assess any additional control measures and validation work required in addition to the normal release requirements and ensure before hand that the product will comply with all regulatory requirements.

All retreatments should have acceptable implications regarding Safety, Health and Environment. An investigation must be conducted to determine the cause of the retreatment and remedial action shall be taken to prevent recurrence.

Retreated product that fails to meet specification or release criteria should not be retreated for a second time if the failure is the same reason as for the original retreatment. The only exceptions are:

- (i) For a failure associated with physical size reduction (e.g. milling and micronising) where further size reduction is permitted
- (ii) For API or intermediate reprocessing providing that the reason for the reprocessing failure is understood and there is evidence that further reprocessing will give acceptable quality product.

5.3 Control of Retreated Products

A regulatory implication assessment may be required before any product resulting from a retreatment activity can be considered suitable for sale.

Any batch of product that has undergone a retreatment procedure must be clearly identified in its batch documentation prior to the formal documentation review by QA.

Retreated batches whether bulk, formulated or packed stock must conform to all established specifications. Any possible market restrictions imposed by regulatory authorities must be considered before release of the product.

Product that has exceeded its shelf life/expiry date should not be retreated under normal circumstances. However, Active Pharmaceutical Ingredients and intermediates may be reprocessed after their allotted retest date according to Procedure 'Determination of Storage Periods for APIs, Excipients, Intermediates and Raw materials'.

5.5.2 Reprocessing

Blending of tailings (small quantities of isolated API or intermediate) is acceptable and is considered as reprocessing.

5.5.3 Reworking

Since reworking involves a process that may not be covered by the registered process description API or intermediate obtained by reworking may not be used commercially until approval of the authorities has been obtained; see section 5.3.

Any rework must be supported by an appropriate evaluation and documentation demonstrating equivalent quality to that produced by original process; see section 5.2. Concurrent validation allows for a more in-depth assessment of a reworked batch and must be used for any API or intermediate rework unless sufficient batches shall be reworked to allow prospective validation. Where routine analytical methods are inadequate (eg if new impurities or physical forms are suspected) additional testing methods should be used.

5.5.4 Recovery

Recovery of API and intermediates is acceptable providing that there is an approved procedure for recovery and that the recovered API or intermediate meets a suitable specification for its use. The specification is not required to be same specification as original (un-recovered) API or intermediate provided that it is suitable to control the quality of the finished API (i.e. raw material for formulation) to its established specification.

5.6 Tablet Products

Where the retreatment activity does not alter the physical or chemical constitution of the product, (e.g. check weighing, hand picking), the process should be validated and then testing may be restricted to those tests, which verify that the retreatment has been successful in removing the defect to a satisfactory level.

This will involve a suitable sampling protocol and check test, (e.g. weighing, visual inspection). However, some retreatment procedures may affect the average physical characteristics of the batch, (e.g. check weighing a batch for low weight tablets could alter mean weight), and suitable checks must be carried out in these cases.

When the reprocessing activity is simply a repeat of a previous unit operation, (e.g. re-drying), testing may be restricted to repeating the normal in-process controls applied to that unit operation.

Any retreatment activity that includes altering the chemical and/or physical constitution of the product (e.g. slugging and recompressing, milling and blending with new manufacture, adding extra lubricant, recoating) is not permitted.