

1 Purpose

The purpose of this guideline is to describe the requirements for the sampling and storage of reference and retention samples under GMP regulations/legislation. Local regulatory requirements that require the retention of additional samples, increased sample quantities or longer retention periods, take precedence over this guideline.

2 Scope and Applicability

This guideline covers GMP samples of Active Pharmaceutical Ingredients (APIs) Raw Materials, Excipients, Intermediates, Bulk Investigational Medicinal Products (Bulk IMP), Packaging Materials and Drug Delivery Systems, and Packaged Investigational Medicinal Products (Packaged IMP) including comparators, related to Clinical Trials. Medical Devices are not included within the scope of this document.

Bio-equivalence/bio-availability samples and method validation samples are included within this guideline.

Samples are retained to fulfill several purposes; to provide a sample for analytical testing, in order to help investigate deviations/complaints as needed, to provide a sample to the Competent Authority if requested.

This guideline applies to all manufacturing and R&D sites and should be applied to contractors sites when working on behalf of the sponsor company.

3 Definitions

3.1 Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

3.2 Excipients

Any material that is used in the manufacture of a Formulated Product that excludes the active ingredient; an excipient may be used during processing but not be present in the final formulation, e.g. Water.

3.3 Intermediate

Material produced during manufacture that undergoes further change or purification. Intermediates may or may not be isolated.

3.13 Packaged Investigational Medicinal Product (Packaged IMP)

A formulated product which has undergone all stages of production including packaging in its final container.

3.14 Pivotal Bioequivalence Study

A study conducted to demonstrate bio-equivalence between the clinical trial formulation on which substantial evidence of safety and effectiveness has been generated and the proposed sales formulation to support an NDA/MAA.

3.15 Reference sample (Reserve sample)

A sample of a batch of API, excipients, packaging material, or bulk or packaged IMP which is stored for the purpose of being analyzed should the need arise during the shelf life of the batch concerned. The reference sample shall be stored in the same container closure system in which the product is packaged or shipped, or in one that has essentially the same characteristics, (i.e. mimics the container-closure system). The IMP reference sample may be taken after manufacturing or after primary or secondary packaging.

3.16 Reference standard for BE Studies

The drug product against which the test article is being tested. This is either, (1) the drug product that was used in the clinical studies demonstrating substantial evidence of safety and effectiveness for the test article's claimed indication, or (2) the marketed product in the case where the test article is being compared to the originator/reference product to establish bio-equivalence.

3.17 Retention sample

A sample of a unit from a batch of packaged IMP. It is typically trial specific and stored for visual identification purposes should the need arise during the shelf life of the batch concerned. This sample can be a physical specimen or an electronic file or photograph based on local legislative and regulatory requirements, and may only be required once per trial.

3.18 Test Article for BE Studies

The drug product for which a company is seeking NDA/MAA approval or supplemental application, e.g. the proposed sales formulation.

4 Responsibilities

It is the responsibility of each site to have procedures in place which comply with this guideline and with local legislative or regulatory requirements where they are different.

The responsibility for the retention of all reference samples lies with the site responsible for analyzing and releasing the materials. This guideline serves

code technology are in place to provide assurance of segregation of products and labels.

5.2 Reference Samples

If a reference sample is taken after the secondary packaging of a IMP, the sample can serve as both a reference and retention sample provided an adequate sample quantity is pulled.

5.2.1 Raw Materials, Excipients, API's, Intermediates, and Formulated Products (Bulk IMP)

The reference sample for excipients, APIs and bulk IMP should consist of at least twice the quantity necessary for all analytical tests required to determine its compliance with specification, except for sterility and pyrogen testing; where the quantity required to repeat these tests only once should be retained. These samples should be retained as described in Appendix A. There is no requirement to retain raw materials or intermediates.

Reference samples need not be taken for excipients such as water, gases or other materials that are highly corrosive or very inflammable unless stated specifically.

5.2.2 Packaged IMP

A packaged IMP reference sample is not mandatory if a bulk IMP reference sample has been pulled in the same CCS, unless required by local regulations. The reference sample should be contained in its primary packaging or in the CCS composed of the same material as the primary container in which the product is distributed.

5.2.3 Comparators and Diluents

Samples of comparators are only required if the comparator is physically manipulated or packaged in an alternative container/closure system. Sampling requirements are per 5.2.1 for bulk IMP. Samples of diluents are only required if they are physically manipulated.

5.2.4 Packaging Material

Reference samples need to be taken from primary and printed packaging materials, unless retained as packaged IMP. Any overprinting, such as batch /lot and expiry date should be included as part of the reference sample. This can be included as a sample retained in the associated packaging documentation.

5.2.5 Storage

Reference samples should be retained and stored under conditions consistent with the product labeling and SLIFE. Reference samples should be securely stored in facilities where the storage conditions are monitored, and segregated from other materials. Samples should be stored in the orientation directed on labeled product.

Samples should be kept at the testing facility where the study is conducted or at an approved contractor site. The study sponsor should provide the testing facility with a supply of the test article and the reference standard sufficient to complete the study and retain the appropriate number of dosage units as reference samples. The study sponsor should not separate out the samples to be reserved prior to sending the batches to the testing facility. The testing facility will randomly select the Reference samples from the supply sent by the sponsor. This is to ensure that Reference samples are in fact representative of the same batches provided by the study sponsor for the testing. In general, the testing facility should retain enough quantity to permit regulatory authorities to perform five times all of the release tests required in the application.

To reduce risk, it is recommended that an additional sample of the same size should be maintained by the sponsor. These materials will be retained for testing by the company if necessary, to confirm the FDA test results under conditions specified by the labeling.

5.5 Reference Samples From Batches Used in Analytical Method Bio-batch Validation (For US NDA only)

Retain 4 X samples of the API and drug product proposed for marketing, each sufficient to permit performance of three times each test described in the sponsor's application until one year after a successful pre-approval inspection.

5.6 Reference and Retention Samples in the Case of Closedown of a Manufacturer

Where a contractor or company sister manufacturing site closes down and the Investigational Medicinal Products (IMP) Manufacturing Authorization is surrendered, revoked, or ceases to exist, it is probable that many unexpired batches of IMP manufactured by that manufacturer will still be in use in clinical trials. In order for those batches to continue to be used in clinical trials, the manufacturer, in collaboration with the CTA or IND holder should make detailed arrangements for transfer of reference and retention samples (and relevant GMP documentation) to an authorized storage site. The CTA/IND holder should, in relation to the suitability of the proposed arrangements for storage of reference and retention samples, consult with the competent authorities of each country, as appropriate, in which any unexpired batch has been placed on the market.