



Handling of Reserve Samples in Pharmaceutical Industries

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ABSTRACT

Reserve samples are important to verify original test results in case there is some doubt about previous test results. Sometimes reserve samples are also important for studies to get additional information and are required by various regulatory bodies. This addresses the process for taking, storing, transporting, and discarding reserve samples.

Keywords: Reserve samples, Pharmaceutical industry, test results.

INTRODUCTION

Handling of reserve samples is intended to provide recommendations for study sponsors and/or drug manufactures, contract research organizations (CROs), site management organizations (SMOs), clinical investigators, and independent third parties regarding the procedure for handling reserve samples from relevant bioavailability (BA) and bioequivalence (BE) as required by 21CFR 320.38 and 320.63.

FDA, Division of Scientific Investigations (DSI) and field investigators from the office of Regulatory Affairs (RA) Conduct inspections of clinical and analytical sites that perform Bioavailability (BA) and be studies for study sponsors and /drug manufacturers seeking approval of generic and new drug products.

A frequent finding from these inspections is the absence of reserve samples at the testing facilities where the studies are conducted. In many cases, Division of Scientific Investigations finds that testing facilities return

reserve samples to the study sponsors and/or drug manufacturers, against the direction of the regulations in 21 CFR 320.38 and 320.63. In other cases, study sponsors and/or drug manufacturers, Site Management Organization, or contract packaging facilities designate the study test article and reference standard for each subject, and preclude the testing facilities from randomly selecting representative reserve samples from the supplies.

Division of scientific Investigation also finds that deviations from the regulations more often occur in Bioequivalence studies with pharmacodynamics or clinical endpoints in which the studies are confused with clinical safety or efficacy studies.

Collection of Raw material samples

Ensure the sample in self-sealing (black/white) polythene bag-labelled and send the labelled sample to control sample room. In case of raw material maintain a separate register for reserve sample.

Glossary/Definition

Item	Explanation
Sample	Representative quantity of material extracted from a batch of reference material
Aliquot	Aliquot — An aliquot is a portion of a sample that is representative of the entire sample (see also subsample).
Split Samples	Two or more representative portions taken from a sample or subsample and analysed by different analysts or laboratories. Split samples are used to replicate the measurement of the variable(s) of interest. Also used as Reserve Samples.
Subsample	A representative portion of a sample.
Representative Sample 21CFR210.3	Representative Sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.
Reserve Samples	Samples used for retesting of the original sample if the initial test results is non-conforming (out of specifications). Reserve samples should be taken from the same homogeneous material that was originally collected from the lot, tested, and yielded the out of specification results. Sometimes also called Retention Samples as required by the FDA to be retained for the FDA in case the agency wants to analyse the sample.



Collection of finished samples

Reserve samples of drug product shall be collected for each batch, market order and each type of pack style control samples of drug product shall be collected in the same or simulated containers in which the drug has been actually marketed these shall be coded as Control sample. Equal amount of samples shall be collected over the complete packaging run. The quantity of reserve samples shall be at least twice the quantity necessary to perform complete analysis. Enter the finished product sample details in the control register for reserve sample finished products.

Sampling Techniques

It is recommend that the study sponsor and/or drug manufacturer send to the testing facility batches of the test article and reference standard packaged in such a way that the testing facility can randomly select samples for bioequivalence testing and samples to maintain as reserve samples. This will ensure that the reserve samples are in fact representative of the batches provided by the study sponsor and/or drug manufacturer and that they are retained in the study sponsor's original container. Because the study sponsor and/or drug manufacturer may provide a testing facility with a variety of container sizes and packaging, Food and Drug Administration is flexible in applying the representativeness requirement described in 21 CFR 320.38. For example, any of the following random sampling techniques might be used by the testing facility for the container size and packaging.

Single Container – If a single container of the test article and reference standard are provided to the testing facility, the testing facility should remove a sufficient quantity of the test article and Reference standard from their respective containers to conduct the study; the remainder in each container should be retained as reserve samples in the original containers.

Multiple Containers – If multiple containers of the test article and reference standard are provided to the testing facility, the testing facility should **randomly select** enough containers of the test article and reference standard to conduct the study; the remaining containers of the test article and reference standard should be retained as the reserve sample in the original containers.

Generally, multiple open bottles are discouraged. It encourages the testing facilities to limit the number of open containers retained as study reserves.

Unit dose – If the test article and reference standard are provided to the testing facility in unit dose packaging, the testing facility should **randomly select** a sufficient quantity of unit doses of the test article and reference standard to conduct the study; the remaining unit doses of the test article and of the reference standard should be retained as the reserve samples in the original unit dose packaging. Therefore, it would be inappropriate to

provide the study medications in unit dose packaging and all the reserve samples in bulk containers.

Quantity of Reserve Samples

The quantity of reserve samples should be sufficient to permit the agency to perform five times all of the release tests required in the application or supplemental application.

The rationale for requiring the five times quantity is provided in the final rule. The clinical investigator can obtain the amount that constitutes the five times quantity from the sponsor and/or drug manufacturer.

For solid oral dosage forms (e.g., tablets, capsules), an upper limit of 300 units each for the test article and reference standard can be considered sufficient to meet the five times quantity.

Because the Agency has limited experience with the retention and testing of non-solid oral dosage forms, the Agency is unable to recommend an upper limit for the retention of non-solid oral dosage forms at this time. In the case of a reference standard that is an extemporaneously compounded solution or suspension or a reconstitutable powder, it is recommended that the pure active ingredient and the unconstituted powder be retained. For a multisite Bioavailability or Bioequivalence study, and also recommend that the total amount of reserve samples to be retained across all testing facilities satisfy the five times quantity requirement. Each site is asked to retain a reasonable amount of test article and reference standard to be determined by considering.

- (1) The total number of testing facilities participating in the study,
- (2) The number of subjects expected to be enrolled at each testing facility, and
- (3) A minimum limit (e.g., 5 dose units) for each of the test articles and reference standards.

If the reserve samples from more than one testing facility are transferred to an independent third party for storage, we recommend that the independent third party segregate the reserve samples from the various testing facilities so that any given reserve sample can be unambiguously associated with the testing facility from which it came.

Storage of samples

Reserve samples of raw materials stored up to 6 years from manufacture date of approval of the material. Solvents, gases, water samples will be not kept. Finished product reserve samples shall be retained one year after the expiry date of the product.

Exhibit batch shall be stored up to the regulatory approval. Sample required special storage condition stored as per the requirement sample shall be kept in properly arranged manner for easy traceability.



Issuance of reserve samples

It is required for any analysis or investigation reserve samples request note shall be initiated by concern person as per the requirement reviewed by Deputy Manager Quality Control or his designed for raw material samples/Deputy Manager Quality Assurance or his designed for finished product samples and approved by Senior Manager Quality Assurance.

After the approval senior manager Quality Assurance executive Quality Assurance shall issue the required quantity from reserved samples the issuance details shall be entered in the respective sample of remarks Column of the control register for reserve samples. Reserve samples of finished products shall examined visually at least twice in a year for all commercial batches for evidence of deterioration. Physical appearance and odour of the drug product should be examined during visual inspection.

One batch of a product manufactured in each calendar month shall be considered for visual inspection. Visual inspection shall be done twice in a year for batches selected. For example- Batches manufactured between january2011 to june2012 Considered for visual inspection in june2012 Batches manufactured between july2011 to dec2012 and so on. The batches selected for visual inspection shall be continuously monitored till the specified retention period.

Visual inspection shall be done as per the quantity and pack as given below for vial/ampoule pack- one vial/ampoule for each annual check.

For bottle pack-one bottle for each annual check.

For Blister/strip-one blister/strip [tablets/capsules to be checked]

Result of periodic examination of reserve samples shall be recorded. In Reserve samples visual inspection report register.

Any evidence of reserve samples deterioration shall be investigated and necessary Corrective action and preventive action shall be taken.

Rack number system for reserve samples Room

1] Number the racks individually as R1, R2, and R3 etc.

2] Each rack is divided in to rows as 1, 2, and 3 etc.

At least separate racks for raw materials and finished products.

Destruction of reserve sample

Every month Quality Control analyst shall review the control register of reserve sample if any sample crossed the retention period.

On completion of retention period get the authorization from senior manager Quality Assurance or his designee in the control register of reserve sample for disposal of reserve sample. After the expiry of raw materials 1finished product collect all the samples & store separately. The details of expired products, materials waiting for destruction should be entered in the register. Upon approval from Quality Assurance quality control analyst shall destroy the sample by referring sop number xxx. Destruction of reserve samples of finished product/raw materials and enter the disposed of date with date with signature on relevant reserve samples control register.

CONCLUSION

Sufficient samples of each batch of pharmaceutical products used in studies, together with the record of their analysis & characteristics must be kept for reference purpose under appropriate storage conditions as specified in national regulations. No need to retain the reserve samples of rejected samples or volatile. Solvent/gases/water used in manufacturing process or hazardous materials (acid, alkalis etc.), flavours, liquid raw material & excipients.

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