

FDA Guidelines-For Out of Specifications (OOS) In Industries

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Abstract: Testing lies at the heart of drug manufacturer's successful operation. Laboratory testing, which is required by the CGMP regulations is obligatory to confirm that components, containers and closures, in-process materials, and finished products conform to specifications, including stability specifications. Testing also supports analytical and process validation efforts. CGMP regulations specifies that finished drug products that fail to convene established standards, specifications, or other relevant quality control criteria will be rejected. Any unexplained inconsistency of the failure of a batch or any of its contents to meet any of its specifications and that tests result that fall out of specifications (OOS) shall be thoroughly investigated, whether or not the batch has already been distributed. For the release of test batch OOS investigation is mandatory. If the OOS is confirmed the batch is rejected and if the OOS is found inconclusive then QA may be able to justify and release the batch.

Key words: cGMP regulations, OOS, Quality control unit, Batch rejection.

INTRODUCTION:

It provides agency's current thinking on out of specification and test results. Purpose of this document is it includes results of all tests that fall under outside of the specification which are established in drug application, official compendia and drug master files or by the manufacturer.

It also applies for all in process tests and chemistry based laboratory testing. Traditional testing and release methods are directed. Laboratory testing are performed under the active pharmaceutical ingredient, other components like in-process materials and finished product materials apply to the extent of current good manufacturing practices regulation and food and drug cosmetic act¹.

This guidance covers the following:

1. Finished products & active pharmaceutical ingredients
2. Biology and biotechnological products
3. Human drugs
4. Veterinary drugs
5. Combination of product
6. Type A medicated articles
7. Medicated feed
8. Dietary supplements
9. Transplantation of human tissues under 361 section

DISCUSSION:

Background and purpose:

FDA announced pharmaceutical CGMPs in August 2002. In that FDA explained agency's quality risk management and its approaches to its existing programs with the goal of industry encouragement to adopt innovative and modern technologies. CGMP regulations are required for conform laboratory that components, in-process and finished product materials and container and closures conform to stability specifications².

Testing also supports process validation and analytical validation efforts. It is generally covers the laboratory operations, laboratory controls and records and reports. These regulations are provided for the establishment of scientifically approved and appropriate specifications, test procedures and its standards that are designed to ensure that the components in- process and finished product conform the standards³. In GMP regulation Section 211.165 specifies that finished products are fail to meet the established standards, quality control tests and specification that products will be rejected.

Under section 501(a) 2(b) both active pharmaceutical ingredient and finished pharmaceuticals are manufactured in accordance with current good manufacturing practices.

Current good manufacturing practices for active pharmaceutical ingredients raw material testing, in-process and stability testing and process validation.

Goal for the guidance:

It describes the quality system model if it implemented it will allow the manufacturers to support modern quality systems that are with the CGMPs. The guidance demonstrates that where this model can fit within the CGMPs requirements. CGMPs requirement flexibility should implement a quality system. This guidance is serving a bridge between the 1978 regulation and current quality systems. For number of reasons this guidance is issued.

Quality system addresses the private and public sector. It have goal to provide quality of drug products to prescribers and patients. A well build quality system should reduce the returned products, recalls, defective products entered into the market.

CGMP regulations are harmonized to extent that possible with the other widely used quality systems. This guidance highlights the common elements between the quality systems and current good manufacturing regulations. With the globalization of pharmaceutical manufacturing system increase the prevalence of combination drugs and biological products. Principles of quality management systems are spread across the different regions and various products.

FDA has concluded that the modern quality management systems are coupled with manufacturing practices effective risk management practices, product knowledge and it can handle many types of changes to equipments, facilities, processes without approval of the regulatory submissions. Manufacturers with a process knowledge and robust system it can implement many types of improvements. Quality system is addition to this by lowering the manufacturing problems risks may result in FDA inspections.

Quality system provides the frame work to implement the quality by design, risk management in the drug manufacturing process⁴.

Scope of the guidance:

This applies for manufacturers drug products. Products are regulated by a center for veterinary medicine, center for biological evaluation and research, center for drug evaluation and research. It is also useful for manufacturer of components used in manufacturing of products⁵. It is not intended to create new requirements for manufacturing of pharmaceutical products that are established in current regulations. It explains comprehensive quality system implementation it can help manufacturers achieve compliance with CGMP regulations.

Organization of this guidance:

It provides reference to industry and quality system models. Major section of the model includes the following:

1. Resources
2. Manufacturing operations
3. Management responsibilities
4. Evaluation activities

Under these systems key elements are found and they are discussed. When an element correlate with the current good manufacturing practices requirement that element associated will be noted. CGMP regulation will be discussed in some cases ⁶.

Identifying and assessing the OOS test results:

Phase 1: Laboratory investigation:

FDA regulations are required for conduction of investigation when OOS results are obtained. To determine the cause of OOS result this investigation is required ⁷. OOS result can be identified by using abbreviation of manufacturing process or abbreviation of measurement process. Based on this result if a batch is rejected that should be investigated and it is necessary to determine this is associated with other drugs or other batches or not.

The investigation should be through, documented, unbiased, timely, scientifically sound. First phase of that investigation includes the laboratory data. Before discard the test preparation this should be done. By using test preparations Instrument malfunction and laboratory error can be tested. This assessment indicates no meaningful errors ⁸.

Responsibility of analyst:

For achieving accurate laboratory testing results first responsibility is lies with the analyst. He is aware of potential problems which occur during the test process and he will watch the problems which could create in accurate results. According to 211.160(b) (4) the instruments which meet the specifications that are used and these are properly calibrated ⁹.

Those analytical methods have system suitability requirements the system which are not meeting the specification that should not be used. The causes of malfunction should be identified and it should be corrected before decision is made ¹⁰.

Responsibilities of laboratory superior:

OOS result has been identified higher judgment should be timely and objective. The results should indicate problems in the manufacturing process. Immediate assessment should include the test units and re-examination of test results and glass wares used in the preparations. For laboratory error hypothesis it provides more reliability ¹¹.

Part of superior assessment the following should be taken:

1. The test method has to be discussing with the analyst and conformation analyst knowledge and performance of procedure.
2. In the analysis examine the raw-material which is obtained including spectra, chromatograms and identify suspect information or anomalous.
3. Calculations are verified which used to convert raw data values into final values which are appropriate, correct and scientifically sound and also determine if any un validated changes have been made in automated calculation methods.
4. Performances of instruments are conformed.
5. Determine the solvent reagents, other solutions and appropriate reference standards were check whether it met the quality control specifications.
6. Performance of test method evaluated to ensure that the performing according to standards and based on historical data and method validation data.
7. It is documented and records should be preserved of this laboratory assessment.

If the returned samples are examined promptly cause of OOS results should be facilitated ¹². What might happened regarding to hypothesis like instrument malfunction and dissolution error should be tested. Part of laboratory investigation examination of retained solutions should be performed.

Investigation of OOS test results:

Phase 2: full scale OOS investigation:

If the initial judgment does not determine the laboratory error caused to OOS results then full scale OOS investigation should be performed. This investigation consists of laboratory work, process and reviews. That investigation should be identified and root causes should be identified and take corrective action and preventive action to prevent that causes ¹³.

Review of production:

QCU will conduct the investigation and all other departments are also involved in the investigation that could be implicated, including process developments, maintenance, manufacturing, and engineering. Multiple manufacturing sites and all sites which are potentially involved should be included in the investigation¹⁴. Also other potential problems should be identified and investigated.

Additional Laboratory Testing:

Additional laboratory testing includes a full-scale OOS investigation. A number of practices are used during the laboratory phase of an investigation which includes

1. Retesting and
2. Re-sampling.

1. Retesting:

Retesting of a portion of the original sample involves part of the investigation. From the same homogeneous material the sample should be taken for the retesting¹⁵. In case of a liquid it may be from the original unit liquid product or composite of the liquid product; in case of a solid, it may be an additional weighing from the sample composite prepared for the original test.

Situations where retesting is required include investigating testing instrument malfunctions or to identify a possible sample handling problem, ex: a suspected dilution error.

2. Re-sampling:

Analyzing a specimen from any additional units collected as part of the original sampling procedure or from a new sample collected from the batch is involved in the re-sampling. There should be sufficiently large original sample from a batch to accommodate additional testing in the event an OOS result is obtained. Examination of additional specimens should be done in accordance with standard operating procedures and sampling strategies¹⁶⁻¹⁸.

Reporting testing results:

Reporting and interpretation of test results can be done by different practices, which include

- Averaging
- Outlier tests.

Averaging:

Together appropriate and inappropriate uses of averaging test data are included during OOS investigation and original testing are there in averaging:

Appropriate uses:

- Averaging data usage depends upon the sample and its purpose. More accurate results can be obtained using averages if sample is homogeneous.
- USP recommends the use of averages for microbiological assays as they have innate variability in the biological test system¹⁹.

Inappropriate:

- Confidence on averaging has the disadvantage of smacking variability among individual test results. For this reason, all single test results should normally be reported as separate values.

Outlier Tests:

- CGMP guidelines prefer that statistically effective quality control criteria should include suitable acceptance and/ or rejection levels.
- Outlier outcomes in a deviation from set test methods.
- Reason for an outlier is due to the fault in the testing procedure and not due to the characteristic variability in the sample being tested.
- This testing is numerical to recognize those that are extreme from an array. Of outlier test should be written into SOPs for data explanation and be well documented. Specific outlier test to be applied with relevant parameters stated in advance are to be included in SOPs. These should also state the minimum

number of outcomes required to obtain a statistically important assessment from the stated outlier test²⁰⁻²⁴.

CONCLUSION:

In this test, the batch quality should be determined, the results should be assessed, and a release conclusion should be made by the QCU. In this case SOPs should be followed in incoming at this point. There is no limit to advance testing to determine the cause of the failure, when a batch has been rejected.

Interpretation of Investigation Results:

- Interpreting the consequences of the investigation will be done by QCU. Conclusion (rejection or failure of batch) should not be taken based on the early OOS results.
- If the supposed result is invalidated then the outcome should not be used to assess the quality of the batch or lot. Invalidation of the distinct test result rest on only up on the observation and documentation of a test result.
- OOS result gives a sign that the batch does not meet required qualifications and this outcome in batch's rejection, in accordance with 211.65 (f), and appropriate disposition. For insufficient investigations OOS result should be given at most important in the batch or lot disposition conclusion.
- In case when OOS was modified, the investigation will changes from an OOS study into a batch failure investigation, which must be extended to other batches associated with the exact failure²⁵⁻²⁸.
- If OOS was not modified (inconclusive), the QCU might still finally decide to release the batch.

Field alert Reports:

- Products which are accepted and shortened new drug submissions require submitting a field alert report within 3 employed days.
- A Field alert report comprises facts concerning any failure of a distributed batch to meet any essential conditions.
- If the OOS result on the dispersed was found to be unacceptable within 3 days, an initial FAR should be submitted. When the OOS examination is completed a track-up Field alert reports (FAR) should be submitted²⁹⁻³⁰.

Acknowledgement: The authors are thankful to JSS College of Pharmacy, JSS University, and Mysore for their valuable efforts in giving a platform to present our work.

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