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OOS: Back to Basics

Even with the number of trainings, seminars, online webinars and consultant guided investigations, companies are still seeing FDA 483 observations around how they are handling and investigating out of specification (OOS) results. The most common reason for this could be a basic misunderstanding of what is actually required in these investigations and how firms are determining the disposition of the product(s) involved.

In order to understand how and what to investigate, it is important to go back to the basics and evaluate what actually defines an OOS result and why the regulatory agencies consider an OOS result a critical failure that needs prompt investigation. An OOS result (often abbreviated as spec) is an explicit set of requirements to be satisfied by a material, product, or service. Should a material, product or service fail to meet one or more of the applicable specifications, it may be referred to as being out of specification; the abbreviation OOS is generally used. The FDA defines the OOS result in CFR part 211.192:

- "Any unexplained discrepancy of the failure of a batch or any of its contents to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed."
- "The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy.
- A written record of the investigation shall be made and shall include the conclusions and follow-up."

The purpose of the investigation is to determine the cause of the OOS result. The source of the result should be identified either as an aberration of the measurement

process or the manufacturing process. Even if a batch is rejected based on an OOS result, the investigation is necessary to determine if the results other products.

In September of 1993, there was a landmark case that set the standard for all OOS investigations in the future: Barr Laboratories, LLC vs. USA. In regulatory action initiated by FDA, a federal court in New Jersey ordered Barr Laboratories to recall millions of its tablets and other drug products. The court found these products had failed to meet quality requirements. FDA initiated the action under the Federal Food, Drug, and Cosmetic Act. To take such items off the market in the past, either the involved firm voluntarily recalled the products, or FDA requested courts to order seizure by U.S. marshals --provided the agency could find the products. Now, with this precedent-setting decision, FDA can ask the court to order the responsible firms to recall. This is known simply to most pharmaceutical firms as the "Barr Decision" and it is the basis for the FDA Guidance on Investigating OOS Results. In short, FDA requires that:

- Finished Pharmaceuticals (DP) and Active Pharmaceutical Ingredients (APIs) to be manufactured in accordance with current good manufacturing practice under section 501(a)(2)(B) of the Act.
- Current good manufacturing practice for APIs includes the performance of scientifically sound Raw material testing, In-process monitoring, Release and stability testing, Process validation, and adequate investigations of any OOS result obtained from such testing.
- The responsibility of a contract testing laboratory in meeting these requirements is equivalent to that of a manufacturing firm.

Once an OOS result is generated there are 2 phases of the investigation. The first phase is the Laboratory Investigation. The first phase includes:

- Assessment of the accuracy of the laboratory's data.

- The investigation should be thorough, timely, unbiased, well-documented, and scientifically sound.
- Test preparations (including the composite or the homogenous source of the aliquot tested) are not to be discarded as they are necessary for investigation
- For contract laboratories, the laboratory should convey its data, findings, and supporting documentation to the manufacturing firm's Quality Control Unit (QA), who should then initiate the full-scale OOS investigation.

During the course of the lab investigation, it is imperative that the lab supervisor perform a thorough investigation. Some vital responsibilities include:

1. Discuss the method with analysts
2. Examine raw data
3. Verify calculations
4. Confirm performance of instruments.
5. Confirm reference standards, reagents
6. Evaluate performance of method
7. Document (most important)
8. Must prove your hypothesis

In summary, when clear evidence of laboratory error exists, laboratory testing results should be invalidated.

When evidence of laboratory error remains unclear, a full-scale OOS investigation should be conducted by the manufacturing firm to determine what caused the unexpected results. This is commonly referred to as Phase II. The objective of such an investigation should be to identify the root cause of the OOS result and take appropriate corrective and preventative action. The key is to unlock the OOS problem which includes a complete review of all manufacturing and process

development documents with a written record of the review. In addition, the firm should review all documents and records of the manufacturing process.

Phase II investigations may also include re-testing/re-sampling. A retest is another test of a portion of the original sample brought into the lab. When it is determined by the firm to perform a retest, there are a few things to remember:

- FDA prefers a second analysts do the retest.
- Don't "test into compliance."
- Specify the number of retests.
- Prepare a protocol before retesting.
- If the error is found the retest substitutes.

As the investigation continues, it is important to remember that once re-testing is decided upon, one may not "test into compliance." Testing into compliance is the practice of ignoring valid information that should be used to make decisions. Such a practice is at best not scientific and at worst is fraudulent, illegal, and immoral. Such practices must be found and stopped.

One other important variable to be cognizant of is the practice of "averaging" results. Even with tests that result in replicate values, it is not wise to average the results. The Quality Assurance Unit must see all of the reportable values. In the event, one replicate is OOS and one is passing, don't average the OOS result with in-specification results.

Upon conclusion of the investigation, if a cause is found, invalidate the initial result and use the retest value(s) in its place. If the OOS is confirmed the batch is rejected. If the OOS is inconclusive and the retests are within specification, then QA may be able to justify releasing the batch.

If the OOS investigation confirms the OOS result and is successful in identifying its root cause, the OOS investigation may be terminated and the product rejected. However, a failure investigation that extends to other batches or products that may have been associated with the specific failure must be completed (§211.192). If any material was reprocessed after additional testing, the investigation should include comments and the signatures of appropriate production and quality control personnel. OOS results may indicate a flaw in product or process design. It is essential that redesign of the product or process be undertaken to ensure reproducible product quality.

About the Author: Danielle DeLucy, MS, is owner of ASA Training and Consulting, LLC which provides Pharmaceutical and Biologics based companies with training and quality systems assistance in order to meet Regulatory compliance. Prior to this role, Danielle has been in the industry for 15 years serving in numerous Quality Management Roles, such as the Director of Product Quality, the oversight of Sterility Assurance practices and provided QA oversight of numerous filling and packaging operations. Danielle began her QA career as a Quality Control Pharmaceutical Microbiologist at a contract laboratory where she performed various tests for their clients. In the years after, she has held positions in the Quality management arena while increasing her responsibility. She has helped to lead many Regulatory Health Inspections and was instrumental in the coaching process of her peers prior to any inspection. Currently, Danielle assists companies who are faced with warning letters, consent decrees and those wishing to improve compliance establish more robust quality systems so that the company can succeed.