
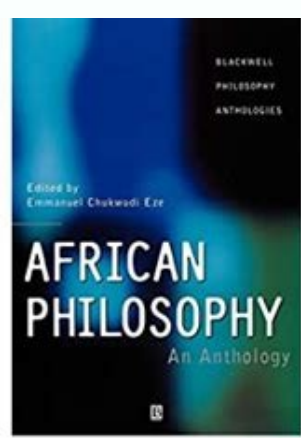


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Investigation of Out-of-Specification Results

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Figure 1. A photograph of a laboratory setting with various pieces of scientific equipment and glassware.

When out-of-specification investigations of a testing error or warning letters issued by FDA (1) occur, workshops, reviews, consultations, and guidelines are available, yet different and inconsistent approaches to out-of-specification investigations prevail. These inconsistent practices and various degrees of a misunderstanding of current expectations in the area have led to more diverse approaches to investigating out-of-specification results. For this reason, the Analytical Research and Development Steering Committee of the Pharmaceutical Research and Manufacturers of America (PhRMA) included the topic of investigating out-of-specification investigations in its annual meeting held in September 2003. Representatives from PhRMA member companies met to consider this topic, share current practices, and agree on an acceptable and replicable (AAR) that represents good science and addresses to current regulatory guidelines and expectations. The output of that meeting is presented in this article.

Background
The guiding principles for out-of-specification investigations are based on a legal ruling by Judge Wilkie in 1999 (2) and the subsequent guidance that followed in September 2000 (3). Judge Wilkie pronounced a case brought by FDA and its state action against a generic-drug manufacturer. Among the issues that were raised were averaging out-of-specification values with in-specification values to get a passing result, maintaining an ineffective program for process validation, clearing up data concerning multiple errors with no defined end point, performing inadequate failure investigations, and lacking needed validation. Judge Wilkie's responsibility was to have to report these facts and craft an opinion that was based on the evidence and the law. In addition, he had to interpret the current regulations along good manufacturing practices.

The trial itself generated 2300 pages of testimony and 400 exhibits and declarations. Judge Wilkie acknowledged that the pharmaceutical industry is a business that operates because of regulations. He also acknowledged the very important task that FDA has as regulator of the industry. The judge found that the company was not in compliance and conflicting opinions about good manufacturing practices and processes a violation were made by the court.

The final decision reflects good science. The judge stated that the history of the product must be considered when evaluating the analytical needs and making a determination

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