

OOS Final Guidance: What Has Changed?

Eight Years in the Making, the Final Guide is Published

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On September 30, 1998, the U.S. FDA announced in the *Federal Register* the availability of a draft guidance, *Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production*. Interested persons were given the opportunity to submit comments by November 30, 1998.

On October 12, 2006, FDA announced the availability of the final guidance in the *Federal Register*. In response to the comments received, the agency made a number of revisions, reorganizations and clarifications in the document. Not many sections of the document were spared revision.

The "Scope" and "Background" are revised to provide more clarity regarding the applicability of the document. The sections "Investigating OOS Test Results—Phase II: Fullscale OOS Investigation" and "Concluding the Investigation" are reorganized. In additions, a number of issues addressed in the guidance are further clarified or include more specific guidance.

This final version provides guidance to the pharmaceutical industry on investigation of laboratory results that fall outside of specification limits. The guidance addresses investigations of OOS results in the laboratory phase, including responsibilities of the analyst and supervisor, and when indicated, the expansion of an investigation outside of the laboratory to include production processes and raw materials as appropriate.

This guidance is intended to apply to traditional methods of drug product testing and release, based on testing of discrete samples of in-process materials and finished products.

What's Out?

There are many minor changes and word substitutions. For instance, the

use of the term "failure" investigation has been removed and the term "OOS" or "full scale" investigation has been substituted. The use of "supervisor" has been replaced with "laboratory management." In addition the term "the overall quality assurance program" has been replaced with "the laboratory quality assurance program."

FDA elected to replace "statistical errors" with "calculation errors."

The sentence, "A resampling of the batch should be conducted if the investigation shows that the original sample was not representative of the batch" has been removed.

This paragraph has been removed: "Statistical treatment of data should not be used to invalidate a discrete chemical test result. In very rare occasions and only after a full investigation has failed to reveal the cause of the OOS result, a statistical analysis may be valuable as one assessment of the probability of the OOS result as discordant, and for providing perspective on the result in the overall evaluation of the quality of the batch."

What's New?

The "Introduction" section contains new language, much of which reflects regulatory developments since the 1998 draft was released, particularly the push for better in-process controls. For example, the following sentence was added: "The term [OOS] also applies to all in-process laboratory tests that are outside of established specifications." A footnote indicates this does not apply to adjustments to prevent process drift. In addition, a large paragraph has been added relative to process analytical technology (PAT). "This guidance is not intended to address PAT approaches, as routine in-process use of these methods might include other considerations."

Additional clarifications in the "Introduction" include the notation that laboratory testing is to be "chemistry-based" and "of drugs regulated by CDER." The regulatory references were expanded to include, "the Federal Food, Drug, and Cosmetic Act (the Act) (section 501(a)(2)(B))." Further, "The principles in this guidance also apply to in-house testing of drug product compounds that are purchased by a firm."

In the "Background" section, FDA added a paragraph noting that API's are to be covered by this guidance as well as finished products, referencing ICH Q7A which was finalized after the publication of the OOS draft guidance.

The agency also stressed the responsibilities of contract laboratories with respect to OOS investigations: "For contract laboratories, the laboratory should convey its data, finding, and supporting documentation to the manufacturing firms' quality control unit (QCU), who should then initiate the full-scale OOS investigation."

The next section, "Identifying and Assessing OSS Test Results—Phase I: Laboratory investigation," FDA added an additional step to the supervisor's assessment: "Verify that the calculations use to convert raw data values into a final test result are scientifically sound, appropriate, and correct; also determine if unauthorized or unvalidated changes have been made to automated calculation methods."

In the following section on the full-scale investigation, FDA clarified that all relevant sites must be included: "In cases where manufacturing occurs off-site (i.e., performed by a contract manufacturer or at multiple manufacturing sites) all sites potentially involved should be included in the investigation."

The potential culpability of product or process redesign is addressed in this section in the new paragraph: "OOS results may indicate a flaw in product or process design...In such cases, it is essential that redesign of the product or process be undertaken to ensure reproducible product quality."

The "full-scale investigation" section covers "additional laboratory testing" either through retesting or resampling. Under "retesting," FDA clarified in the final document that, should a second analyst perform the retest, he/she "should be at least as experienced and qualified in the method as the original analyst." Retesting has an additional requirement. "The maximum number of retests to be performed on a sample should be specified in advance in a written standard operating procedure (SOP)...Any deviation from this SOP should be rare...In such cases, before starting additional retesting, a protocol should be prepared that describes the additional testing to be performed and specifies the scientific and/or technical handling of the data."

New statements are included under "resampling": "The original sample from a batch should be sufficiently large to accommodate additional testing in the event an OOS result is obtained. In some situations, however, it may be appropriate to collect a new sample from the batch."

Guidance on "averaging" under the subheading "Reporting Testing Results," was reorganized into two subsections: "Appropriate uses" and "Inappropriate uses."

In "Appropriate uses," FDA includes a reference to a new definition for "reportable results": "The term reportable result as used in this document means a final analytical result. This result is appropriately defined in the written approved test method and derived from one full execution of that method, starting from the original sample." This is in accord

with industry literature and the United States Pharmacopeia definition. Two additional paragraphs expand on the concept. Included is the new expectation that the variability of the replicates will have acceptance criteria and that "If acceptance limits for replicate variability are not met, the test results should not be used."

Under "Inappropriate uses," the misuse of averaging is expanded in two new paragraphs.

The section on "Interpretation of Investigation Results" has been expanded considerably with five new paragraphs. Interestingly, while the guidance does not give recommendations for the sample size for retesting, the example scenario given uses seven retests. Seven was the suggestion in a footnote in the Barr Case judgment. The sample size question is still unresolved.

A new section titled "Cautions" has been added. The first paragraph

continues a discussion of reportable results stating that "...a firm should err on the side of caution..." The second paragraph adds a new issue to the guidance, noting that a low assay result should raise concern and that "One cause of the result could be that the batch was not formulated properly. Batches must be formulated with the intent to provide not less than 100 percent of the labeled or established amount of active ingredient." While this is an old GMP concept, it is interesting that it is expressed here in this context.

Conclusion

The final guidance is welcomed by the industry for addressing several issues that had not been resolved. However, there are still issues that need to be the subject of ongoing dialog between FDA and the industry. The final guidance provides a firm platform on which to build those discussions. ☺



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