OUT OF SPECIFICATION (OOS) AND OUT OF TREND (OOT) RESULTS

by Pete Gough

The issue of OOS results first came to prominence with the Barr case nearly 20 years ago. In spite of the fact that Judge Wolin gave his landmark ruling back in February 1993 companies are still failing to meet the expectations of regulatory authorities in this vital compliance area.

In the first half of 2011 the US FDA issued no fewer than five Warning Letters to companies for failing to adequately investigate and follow up OOS results as part of the batch release process. The companies, based in Sweden, Israel, Spain, Mexico and Germany are all global organisations and include generics.

Since the Barr case the US FDA has led the way in defining standards for the investigation of OOS results, culminating in the publication of the final Guidance for Industry on this subject in October 2006. This American guidance has become the generally accepted global standard but in 2010 the UK MHRA published its own guidance as not all pharmaceutical quality control laboratories were following the accepted practice when OOS results occurred. Although it is less detailed, in general the MHRA guideline is compatible with that of the FDA and it improves upon it in some areas.

Both the US and the UK guidance make it clear that the investigation process to be followed should be the same for analytical results that are OOS, OOT or indeed for any result that is outside the usual pattern of results (often referred to as atypical results). In order to be able to identify OOT and atypical results it is essential that laboratory results are continuously trended in some way. For release test results this is normally accomplished by plotting them on a control chart and for stability programme results by plotting the regression line.

The investigation process flow is similar in the US and UK guides; an initial laboratory investigation which, if inconclusive, is followed by an investigation in production and possible additional laboratory testing.

In order that laboratories can perform a meaningful investigation following an OOS or OOT result, it is essential that all apparatus and instruments are preserved after finishing the analysis until after the results have been checked against both the applicable specification and the normal pattern of results. If an OOS or OOT result is identified, then this must be immediately reported to a supervisor and the initial laboratory investigation started. It is considered appropriate to re-measure previously prepared solutions, providing this is done to support a written hypothesis as to the cause of the suspect result.

If the laboratory investigation identifies an error that justifies invalidating the original result, then this should be documented and the original analysis repeated exactly as per the method; i.e. with no additional replication.

If, on the other hand, the laboratory investigation is inconclusive then the investigation must proceed outside the laboratory. This production investigation should seek to identify any errors or deviations within the manufacture or packaging of the lot that could cause the suspect result. Obviously, if such a production error is identified, the disposition of the batch should be determined on the basis of the original laboratory result.

If the investigation is still inconclusive after the production investigation then, and only then, further testing of the sample originally submitted to the laboratory can be considered. This is defined as re-testing. One issue that caused much debate for many years after the Barr judgement was just how many re-tests should be performed. Judge Wolin proposed that seven would be a reasonable number but gave no justification for this. Many statisticians have looked at this issue in the intervening 18 years and the generally accepted view is that the minimum number of re-

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tests is five if one is to be able to have any degree of confidence when comparing the re-test results to the original results. It is also generally accepted that the law of diminished returns applies once the number of re-tests is over about nine or ten. So it turns out that Judge Wolin was about right! Today, a common practice is to have the original analyst and a more experienced one each run three re-tests, to give a total of six results to compare with the original figure.

Re-sampling, i.e. taking further samples from the bulk batch, is more problematic as it calls into question the validity of a company's sampling plan for all batches. Generally, re-sampling should only be performed where there is evidence to show that the original sample was taken incorrectly or was in some way compromised.

Comparing re-test and original results and making subsequent batch release decisions is a complex area, where the FDA guidance is somewhat inconsistent. Outlier tests may be used to see if the original and re-test results are likely to be from the same population or not. However, even if the original result is statistically shown to be an outlier, this alone is not sufficient reason to discard the result.

The question of the averaging of results is another area that has been contentious. The FDA guidance states that if the registered test consists of replicates to arrive at a result (e.g. replicate HPLC injections or even replicate test preparations) the result from the average response is considered one test and one 'reportable result'. However, when averaging replicates in this way you must establish acceptance limits for the variability of the individual results. If these variability limits are not met the results must not be used and an investigation performed as to why the normal variability was exceeded.

The FDA guidance states "In OOS investigations you should not average original and re-test/re-sample results". The reason for this is that the FDA has always been concerned that averaging can be used to hide variability. However, this statement is not always in accordance with statistical thinking. If the original result is shown to be a statistical outlier when compared to the re-tests, then the FDA statement is correct. However, if the original result is not an outlier then the original result and the re-tests should be averaged to obtain the best estimate of the true result. To exclude

the original result from the calculation of the average in this latter case would introduce an unacceptable bias to the calculated mean.

The concern over averaging concealing variability is overcome if, as well as calculating the mean of the results, you also calculate the 95% confidence interval for the mean. This approach is recommended in the UK MHRA guidance.

NSF's advice is that you need to be very clear in what you register as the reportable result when performing replicate injections or determinations, to reduce the possibility of misinterpretation. We would also recommend that in your OOS procedure you clearly define the rules regarding averaging; i.e. if the OOS result is an outlier it should not be averaged with re-test results and if it is not an outlier then it should, and requires the calculation of the 95% confidence interval in all cases. Lots should only be considered for release if a full investigation has been completed and the whole of the 95% confidence interval is within specification.

It is not unusual for the investigation to be completed and still to be inconclusive as to the reason for the original OOS or OOT value. As each case must be considered individually it is not possible to give

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definitive guidance on how to make the final batch disposition decision. However the following general advice applies – if the investigation is inconclusive and all re-tests meet specification, the lot may be releasable, if:

- There are no production aberrations or unusual variations
- The process and product history show that the process is robust
- The re-test results are all within known variability for method
- The 95% confidence interval of the overall mean is within specification limits
- All other results from lot (e.g. in-process, content uniformity, dissolution) are consistent with the re-test results
- Other factors such as stability and the use of the product are considered

The guidelines from the FDA and MHRA serve as a valuable guidance to any company seeking to develop its approach to dealing with OOS, OOT and atypical results. A company must show that it has a rational and comprehensive approach to dealing with suspect test results. Suspect result investigations and their documentation are vital to the credibility of a laboratory. Failure to follow the OOS/OOT guidelines can call into question the integrity of all of the results generated by a laboratory, with very serious consequences for the company.

OOS/OOT result investigations, together with many other compliance and technical issues for laboratories, will be discussed during the NSF course 'Analysis and Testing' visit **www.nsf.org/info/pharma-training** for more information on the next available course.

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