Out of Tolerance Calibrations – Assessing the Impact

Inspections are critical in demonstrating that product meets applicable acceptance criteria and allowing for product release. These inspections often take place using calibrated monitoring and measuring equipment. But what happens if the inspection / measuring / test equipment is found out of tolerance? What does that mean for product that was previously released using results obtained with that equipment?

This White Paper focuses on assessing the impact of calibrations with out-of-tolerance (OOT) results. It includes a discussion on the following:

- What are the regulatory requirements for OOT results?
- How is an OOT result identified?
- What are the next steps following an OOT result?
- How can an OOT result be prevented?

What are the regulatory requirements for OOT results?

21 CFR 820.72 (b) states:

…When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be documented.

ISO 13485:2016 § 7.6 states:

…the organization shall assess and record the validity of the previous measuring results when the equipment is found not to conform to requirements. The organization shall take appropriate action in regard to the equipment and any product affected.

How is an OOT result identified?

Whether your organization conducts calibrations internally, or whether calibration activities are subcontracted to a third party, it is important to note that any tolerance ranges identified are appropriate for the equipment's intended purpose.

For example, if your organization conducts a sealing operation as part of your product's packaging configuration, the sealing parameters utilized should be within the tolerance of the equipment calibration. This means if the sealing temperature set point is 200°F, the tolerance for the sealing equipment should include that nominal value, plus an appropriate tolerance range (± 4°F, or 196°F - 204°F perhaps). With that tolerance defined, the As-Found calibration result can identify any percent error from the nominal value, and whether the result was within the defined tolerance range. If, for example, the As-Found result for the Temperature Characteristic was set at 200°F and the measured value was 195°F, this would be considered OOT, given the tolerance conditions described above.

What are the next steps following an OOT result?

The next steps after identifying an OOT calibration result depend on what is dictated by the organization's Quality Management System (QMS). One option would be to issue a Nonconformance Report.

Issuance of a Nonconformance Report provides a means for formal documentation of the event within the organization's QMS. This allows for investigation of the event, as well as an assessment of any adverse effect on the device's quality. As part of the investigation, the organization shall document a review of all product produced from the time the OOT was identified, to the date of the previous calibration record reflecting that the equipment was within tolerance.

Continuing with the example provided above, there are potential variables in determining how to assess product impact:

- Is this sealer used to provide a product packaging seal that is critical in maintenance of sterility?

  In this scenario, the manufacturer produces a product which is then sealed into a tray, pouch, etc. The packaged product is subjected to terminal sterilization (Ethylene Oxide,

Gamma Radiation, etc.) and the packaging provides a barrier to microbial contamination of the product, thereby allowing it to maintain its status as sterile product. In this situation, the sealing operation is critical, as a breach in the seal (sterile barrier) will result in a non-sterile product. This further supports that the calibration of the sealing equipment is also critical.

Recommendations for investigation might include the following:

- Identification of products produced since the last successful calibration (within tolerance);
- Inspectional activities performed on products produced that might have helped to identify any issues with the seal integrity;
- Retain samples or any product remaining in inventory to assess the current seal integrity;
- Complaint or Post Market Surveillance activity related to product packaging since the last successful calibration; etc.

- Is this sealer used to provide a product packaging configuration that is critical in support of a packaging validation?

  In this scenario, the manufacturer also produces a product which is then sealed into a tray, pouch or similar. The packaged product represents the configuration which underwent packaging validation. Any breach in the seal might compromise the overall package integrity and the ability of the product to arrive at the end destination (post-shipping) without damage.

  Recommendations for investigation might also include the following (same as above):
  - Identification of products produced since the last successful calibration (within tolerance);
  - Inspectional activities performed on products produced that might have helped to identify any issues with the seal integrity;

- Retain samples or any product remaining in inventory to assess the current seal integrity;
- Complaint or Post Market Surveillance activity related to product packaging since the last successful calibration; etc.

- Is this sealer used to seal ancillary components in a non-critical packaging configuration (neither packaging validation nor sterile barrier applicable)?

  In this last scenario, the manufacturer produces ancillary components which are then sealed into a tray, pouch or similar. The packaging neither supports maintenance of sterility nor any kind of packaging validation. Although investigational activities are still applicable, the risk of the OOT calibration result is lower; thereby, the overall concern for the OOT result is lower.

The outcome of the investigational activities can lead to product recall, in cases where the performance of the equipment was critical and the end result (eg. seal integrity) cannot be verified. Of course, in cases where the equipment performance was noncritical, or results of the operation were otherwise verified, it's possible to document a rationale in the Nonconformance Report to support that product impact was low and product recall is not applicable.

How can an OOT result be prevented?

Use of the following methods (identified within ISO 13485 and 21 CFR820) can help to prevent OOT results:

1. Ensure that inspection, measuring and test equipment is suitable for its intended use and is capable of producing valid results;
2. Establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked and maintained;
3. Ensure that procedures include provisions for handling, preservation and storage of equipment so that its accuracy and fitness for use are maintained;

4. Ensure that procedures include specific directions and limits for accuracy and precision;
5. Perform calibrations at specified intervals (or prior to use);
6. Record any equipment adjustments or readjustments;
7. Safeguard equipment from any adjustments that would invalidate the measurement results;
8. Protect monitoring and measurement equipment from damage and deterioration during handling, maintenance and storage;
9. Utilize calibration standards that are traceable to national or international standards, where possible. If no applicable standard exists, establish and maintain an in-house standard, record the basis used for calibration or verification; and
10. Identify equipment calibration status on or near each piece of equipment.

Summary

Inspection results are relied upon to demonstrate that product meets applicable acceptance criteria. This supports product integrity and enables the release of product into distribution. If; however, monitoring and measurement test equipment are found out of tolerance, product released using that equipment now requires an impact assessment. The depth of the impact assessment requires alignment with the associated risk. In some situations, the risk is low and can be rationalized. In other situations; however, the risk can be high enough to result in product recall. It is important to implement appropriate controls within the QMS and take actions to prevent OOT results.

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