

Beamex

Calibration White Paper

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Calibration in a regulatory environment

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For process manufacturers, regular calibration of instruments is common practice. In areas where instrument accuracy is critical to product quality or safety, for example in process industries such as chemicals and pharmaceuticals, calibration every six months – or even more frequently – is not unusual. In such industries rigid calibration schedules are necessary in order to maintain compliance. Mistakes in calibration records or missed calibration tests are especially costly, as they can result in lost batches, fines, or other sanctions.

The purpose of calibration itself is to determine how accurate an instrument or sensor is. Although most instruments are very accurate these days, regulatory bodies often need to know just how inaccurate a particular instrument is and whether it drifts in and out of specified tolerance over time.

Calibration in the pharmaceutical industry

A small human error or the failure of an instrument in a pharmaceutical plant could adversely affect the health of thousands of people. This is why pharmaceutical manufacturing is one of the most stringent, highly regulated industries in the world. Calibration requirements in this industry are governed by FDA (the US Food and Drug Administration) regulations. In Europe, the corresponding standards are EMEA (European Medicines Agency) and local legislation.

Process measurements are critical in order to ensure product quality. Therefore, calibrating instruments properly in a timely manner is an important aspect of ensuring that a pharmaceutical product is manufactured correctly.

FDA/EMEA regulations state that manufacturers must maintain calibration records and carry out calibration of instruments according to written, approved procedures. In addition, each instrument at the plant must have a master history record, a unique ID and all product, process and

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safety instruments should be physically tagged, sometimes even colour-coded.

The manufacturer must also define a calibration period and error limits for each instrument. Standards should be traceable to both national and international standards. These standards must be more accurate than the required accuracy of the equipment being calibrated. Furthermore, the personnel who carry out the calibration work must be properly trained and competent, with documented evidence of this. A documented change management system must also be implemented.

Regulations

All of the above systems and procedures should be implemented in conjunction with the following regulations: 21 CFR Part 211: “Current Good Manufacturing Practice for Finished Pharmaceuticals” and 21 CFR Part 11: “Electronic Records; Electronic Signatures” or Annex 11 in the EU GMP Guidelines.

As well as FDA/EMEA regulations, which are of course mandatory, voluntary ISO standards exist such as ISO 9001:2008. Under this standard, a company that manufactures pharmaceuticals pays a third party company to audit it to that standard, in order to ensure that it is following its quality manual and is within compliance. A set of guidelines are used to write its quality manual and other standard operating procedures (SOPs).

ISO 17025 ‘General requirements for the competence of testing and calibration laboratories’, for example, applies to all organisations performing tests and/or calibrations, including first, second and third party laboratories, and



laboratories where testing and/or calibration forms part of inspection and product certifications.

Other regulations exist that are relevant to pharmaceuticals companies. The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S), for example, aims to improve harmonisation of Good Manufacturing Practice (GMP) standards and guidance documents.

Other standards and regulations have emerged in response to the increased use of computerised systems for documenting inspection and calibration activities. GAMP, for example, is a Community of Practice (COP) of the International Society for Pharmaceutical Engineering (ISPE), which aims to provide guidance and understanding with regard to GxP computerised systems.

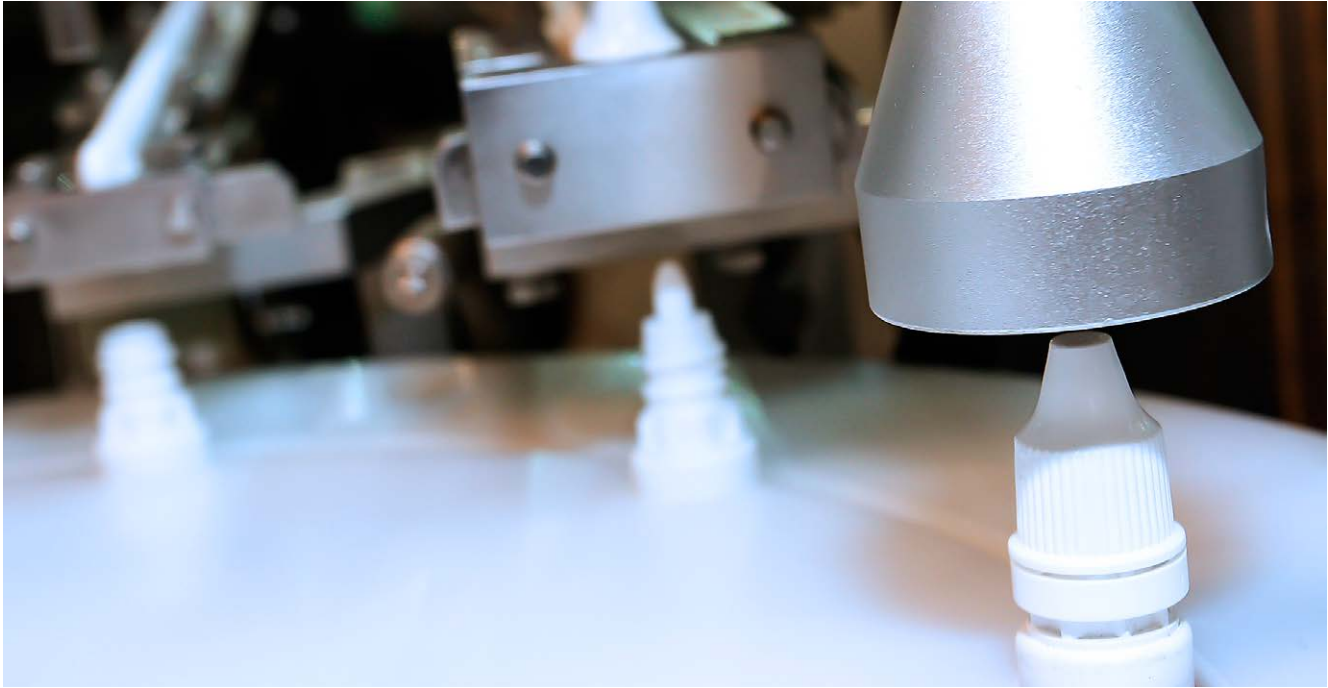
The calibration process

Calibration in a typical pharmaceutical plant is critical, but is often expensive and time-consuming. Meeting all the relevant FDA/EMA regulations and ISO standards is a major contributing factor here, as well as the sheer volume of instruments that need calibrating at regular intervals. Due

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When a plant is being audited, firms that have implemented some sort of calibration management software will find that the preparation and the audit itself are much less stressful. Locating records and verifying that the system works becomes effortless when compared to traditional paper-based record keeping. Calibration management systems therefore improve plant efficiencies because the entire calibration process is streamlined and automated.



Costly production downtime due to unforeseen instrument failures will also be reduced.

The importance of documenting calibrations

Calibrations must be traceable. Traceability is a declaration stating to which national standard a particular instrument has been compared.

The organization itself determines the monitoring and measurements to be performed, as well as the measuring devices needed to provide evidence of a product's conformity to determined standards. The organization also establishes the processes for ensuring that measurements and monitoring are carried out in a manner consistent with the monitoring and measurement requirements. However, the critical final step in any calibration process, documentation, is often neglected or overlooked because of a lack of resources, time constraints, or the pressure of everyday activities.

By using a documenting calibrator, results are automatically stored in the calibrator's memory during the calibration process. The calibration results are then transferred automatically from the calibrator's memory to a database. Users do not have to manually record the results, making the entire process much faster and less costly. Based on the stored calibration records, companies analyze the history

trend reports and can thereby optimize the calibration interval for a certain instrument. Quality and accuracy of calibration results also improve, as there are fewer mistakes due to human error. By integrating calibration software to the calibration process with documenting calibrators, companies save time and improve calibration consistency, as the calibration procedure is fully automated and paperless. Calibration reports and calibration certificates are configurable and available in a paperless electronic signature environment, compliant with the FDA's 21 CFR Part 11.

In order to ensure valid results, measuring equipment is calibrated or verified with measurement standards traceable to national or international standards at specified intervals. If no such standards exist, the basis used for calibration or verification is recorded; adjusted or re-adjusted as necessary; identified for determining the calibration status; safeguarded against adjustments that would invalidate the measurement result; protected from damage and deterioration during handling, maintenance and storage.

In addition, the organization assesses and records the validity of the previous measuring results when the equipment is found not to conform to requirements. The organization then takes appropriate action on the equipment and any product(s) affected.