1.0 Purpose

The objective of the Calibration and Equipment Control process for analytical instruments is to ensure that laboratory monitoring and measuring equipment is appropriately calibrated or verified to ensure the equipment's continuing suitability for use and accuracy of measurements. Another objective is to ensure that maintenance is performed on test equipment to ensure proper functioning.

2.0 Scope

This procedure applies to the analytical control system for the calibration or verification and maintenance of all analytical monitoring and measuring equipment and materials used to perform laboratory activities and generate analytical results. This procedure also ensures that such equipment is used in a manner that is consistent with measurement requirements for the specifications relevant to the laboratory activities concerned. This procedure also applies to the maintenance of analytical equipment which does not require calibration and software used for accredited testing activities.

3.0 Responsibility

3.1 This procedure applies to all employees who use analytical measuring equipment to assess samples for testing finished products, raw materials, or any other samples for a GMP purpose.

3.2 The definition, implementation and maintenance of the calibration system is the responsibility of the Analytical Development Manager, who oversees the Calibration and Equipment Control process.

3.3 The Analytical Development Manager is responsible for and maintains the Calibration Database, calibration certificates, records of calibration and verification activities, maintenance and/or qualification schedules and records of maintenance and qualification activities.

3.4 Personnel who suspect measuring equipment needs calibration or verification or equipment used for testing needs repair or maintenance are responsible for submitting it to, or bringing it to the attention of, the Analytical Development Manager.

3.5 The Analytical Development Manager is responsible for proactively ensuring equipment used for testing is in working condition for its intended use and for maintaining records of equipment maintenance.

3.6 The Analytical Development Manager is responsible for ensuring this procedure is accurate, understood, and implemented effectively. This procedure may not be changed without the authorization of the Analytical Development Manager.

4.0 Definitions

4.1 **Analytical Instrumentation** – instruments/machines used for the procurement of data used in the release of a batch

4.2 **QC** – quality control

4.3 **Calibration** – set of operations which establishes, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system and the corresponding standard or known values

4.4 **GMP** – Good Manufacturing Practices; a system for ensuring that products are consistently produced and controlled according to quality standards

5.0 References

5.1 C-502, SOP, Record Storage, Retention, and Destruction

5.2 D-117, SOP, Laboratory Purchases and Receiving

5.3 D-602, SOP, Labelling and Expiration Dating of Laboratory Chemicals

5.4 G-102, SOP, Equipment Profiles

5.5 G-201, SOP, Calibration Program

5.6 QS-108, SOP, Corrective and Preventative Action.

6.0 Procedure

6.1 Prior to use, calibrated or verified equipment, standards and/or reagents are checked to ensure they are within their valid period of calibration or expiration status as appropriate. No equipment is used if its calibration has expired or if its calibration status cannot be determined. No standard or reagent is used if its expiration date is past due.

6.2 All personnel who use calibrated or verified instruments are trained (or have established experience when hired) in the selection and use of such instruments so they understand the required measurement accuracy and use measuring equipment that is capable of the required precision. Test Methods and internal test procedures identify the measurements required for each test, including the tolerances associated with the required measurements. Test Methods identify the equipment required, measurement equipment required, and methods used to perform Lab testing.

6.3 Personnel do not adjust, nor attempt to calibrate any instruments subject to calibration. Equipment suspected of needing calibration is submitted to, or brought to the attention of, the Analytical Development Manager.

6.4 Calibrated or verified instruments are used, handled, stored, and transported in such a way as to prevent damage, contamination, or deterioration and to protect their integrity. Where possible and applicable, such instruments are safeguarded from adjustments that would invalidate the calibration setting.

6.5 General equipment used to perform testing is maintained in good working order to ensure proper performance. Prior to performing testing, the equipment is verified to ensure it is working, as necessary.

7.0 Procedure

7.1 Process Inputs

7.1.1 Entries in to the Calibration and Equipment Control process include, but are not limited to:

7.1.1.1 Laboratory activities which require calibrated or verified equipment to satisfy requirements of established test standards.

7.1.1.2 Laboratory activities which require functional equipment to perform calibration services.

7.1.1.3 Established test standards which define required equipment specifications, accuracy, and performance.

7.2 Laboratory Environmental Conditions

7.2.1 Where established calibration methods require monitoring and control of environmental conditions, these conditions including but not limited to temperature are measured using calibrated equipment such as a thermocouple meter, calibrated mercury thermometer, or other equipment traceable to appropriate national or international units of measure which apply to the

environmental condition which must be monitored and controlled. The calibrated equipment used for these measurements are included in the calibration control process described in this procedure.

7.2.2 If environmental conditions stray from the required specification, appropriate action is taken. The events which caused environmental conditions to stray is recorded and evaluated, and appropriate corrective action taken as described in the Nonconformity and Corrective Action procedure. Corrective actions taken will consider calibrations being performed when the environmental conditions strayed and the duration of the event which caused the environmental conditions to stray. If investigation of the event indicates the events could recur, actions are taken to prevent recurrence.

7.3 Acquisition of Equipment

7.3.1 The Laboratory Management and/or the Analytical Development Manager ensures the Lab is furnished with all items of measurement and test equipment required for the correct performance of testing services (including environmental monitoring, preparation of test items, processing, and analysis of test data). No testing is performed outside of the Lab's permanent control.

7.3.2 The Analytical Development Manager will act as described in the Purchasing and Receiving procedure (D-117) to acquire measuring and other equipment required to perform calibration services. The following hierarchy of order is used while selecting equipment:

7.3.2.1 Equipment which will satisfy or is specified in requirements of the established calibration method,

7.3.2.2 Equipment with accuracies matching similar equipment,

7.3.2.3 Equipment which achieves performance of stated tolerances as indicated by the equipment manufacturer or calibration certificate.

7.3.3 If equipment is purchased as calibrated or verified, the Laboratory Management or Analytical Development Manager will review the purchasing information communicated to the supplier to ensure that traceability requirements to national or international standards, to make sure that calibration and/or verification requirements and certificate requirements are included, and that the manufacturer is accredited to ISO 17025. If the manufacturer is not accredited to ISO 17025 or is not an allowable exclusion for accreditation, the equipment must be calibrated by an accredited calibration service provider prior to use.

7.3.3.1 If the equipment is purchased as not calibrated (only certified for accuracy or inspection), the equipment is calibrated or verified, as applicable, in-house or by an accredited calibration service provider prior to use.

7.3.4 Upon receipt of newly purchased equipment and prior to initial use, the equipment, and their accompanying certifications (as appropriate) are sent to the Analytical Development Manager. The equipment is evaluated to determine it meets specified requirements for the function it will perform, and the condition of the equipment is assessed to determine if it is in proper working order prior to being put into service. The Analytical Development Manager will add the new equipment to Calibration Database. Equipment will then be moved to the appropriate area for storage or use.

7.3.5 Instruments used during accredited testing are typically identified by a calibration label attached to the equipment or, where appropriate, on the equipment case. Calibration labels show the valid period of calibration (the date calibrated and date due), the service provider who performed the most recent calibration, and the equipment's unique serial number. If labels are not used (e.g., not practical), the equipment's calibration status and information are available according to equipment's Calibration Records and according to their serial numbers.

7.4 Equipment Calibration

7.4.1 Only calibrated or verified equipment is used in testing. Any software and comparative references used during accredited testing will also be periodically confirmed to ensure continuing suitability and effectiveness. Software used during accredited testing is also identified in the Software Validation Log and confirmed using appropriate methods such as data output reviews, known failure testing, etc. In lieu of this, Ion relies on the IQ/OQ performed by the manufacturer.

7.4.2 The Lab maintains metrological traceability of its measurement results by means of a documented unbroken chain of calibrations, each contributing to the measurement uncertainty, and linked to an appropriate reference. The calibration process described in this procedure will maintain metrological traceability and provide records documenting the unbroken chain of calibrations. Measuring equipment is calibrated based on the conditions listed below. Equipment subject to these requirements are identified in the Calibration Database.

7.4.2.1 The measurement accuracy or measurement uncertainty of equipment will affect the validity of the reported laboratory results,

7.4.2.2 When calibration of the equipment is required to establish metrological traceability of the reported calibration services results,

7.4.2.3 Test and measurement equipment is used to control critical calibration functions or acquire calibration data,

7.4.2.4 Test and measurement equipment is used to acquire calibration data.

7.4.3 The various Calibration Database's spreadsheets include the following worksheets as appropriate for their intended use:

7.4.3.1 Change History – records of changes to worksheets.

7.4.3.2 Calibration or Verification – identification of equipment requiring calibration or verification and calibration/verification information.

7.4.3.3 Equipment Maintenance – identification of equipment designated as calibration not required.

7.4.4 The worksheets in the Calibration Database establish the control features necessary to control, calibrate or verify, and maintain monitoring and measurement equipment. Each database includes instrument type (including software or firmware version) or standard, unique identification, manufacturer's name, location, and frequency of checks. Associated certificates of calibration from external calibration services identify the check method and acceptance criteria.

7.4.5 The Lab Management or Analytical Development personnel selects providers of calibration services according to the Purchasing and Receiving procedure, using the same process described for acquiring measuring and other equipment required to perform laboratory operations (see above). All providers of calibration services are required to provide documented evidence (typically in the form of a calibration certificate) of traceability to national or international standards for measurement for each calibration performed.

7.4.6 Prior to selecting a calibration service provider, Lab management or the Analytical Development Manager will ensure the provider maintains a current accreditation to ISO 17025 and has the capability to perform calibrations traceable to the U.S. National Institute of Standards and Technology and the International System of Units (SI), or other national metrology institution.

7.4.6.1 If the calibration service provider does not maintain a current accreditation to ISO 17025, approval by the Lab's accreditation body is required prior to initial use.

7.4.7 All equipment requiring calibration undergoes an initial calibration before being put into service unless it was purchased as calibrated by an accredited calibration service and the equipment is in their scope of accreditation. Thereafter, calibration intervals are determined at a frequency described in the equipment profile that was created according to G-102.

7.4.8 The Analytical Development Manager reviews the Calibration Database on a routine basis to determine equipment due for calibration. When the Calibration Database indicates calibration is required, arrangements are made for calibration to be performed by the selected calibration service provider. If equipment is shipped off site for calibration, actions are taken to protect the equipment from damage while in transit.

7.4.9 When calibration or verification has been completed, the calibration service provider will apply a calibration label to the instrument or standard (or its case) which indicates the date of calibration and the next calibration due date. If it is not feasible to apply a calibration label to the device or its case, identification of calibration status is achieved through other means in the vicinity of the equipment to identify its calibration status.

7.4.10 The calibration service provider will provide a certificate of calibration (or equivalent), indicating the results of the calibration or verification. The Analytical Development Manager will review each certificate to ensure the following data is present (at a minimum) to ensure compliance with ISO 17025:

7.4.10.1 A valid accreditation body endorsement for the calibrations performed in the form of an accreditation body logo. If an accreditation body logo is not present on the calibration certificate, the calibration certificate must contain the following four elements on the first page of the calibration certificate:

- A statement that the calibration meets requirements of ISO 17025,
- The name of the accreditation body which accredited the calibration laboratory,
- Reference to the calibration laboratory's accreditation certificate number, and

- A statement that the calibration is within the calibration laboratory's scope of accreditation.

7.4.10.2 Title (e.g., "Calibration Certificate");

7.4.10.3 Unique identification of the calibration certificate (such as the serial number);

7.4.10.4 The name and address of the laboratory, and the location where the calibrations were carried out (if different from the address of the laboratory);

7.4.10.5 The name and address of the Ion Labs;

7.4.10.6 A description of the condition of and unambiguous identification of the equipment calibrated;

7.4.10.7 The date of receipt of the equipment (if this is critical to the validity and application of the results);

7.4.10.8 The date(s) of performance of the calibration;

7.4.10.9 Reference to the sampling plan and procedures used by the calibration laboratory or other bodies (if these are relevant to the validity or application of the results);

7.4.10.10 Identification of the method used;

7.4.10.11 Evidence that the measurements are traceable to national standards,

7.4.10.12 Acceptance criteria;

7.4.10.13 The uncertainty of measurement and/or a statement of compliance with an identified metrological specification or clauses;

7.4.10.14 Environmental conditions under which the calibrations were made that have an influence on the measurement results;

7.4.10.15 The calibration results, with the units of measurement where appropriate;

7.4.10.16 Description of adjustments made if applicable;

7.4.10.17 The name(s), functions(s) and signature(s) or equivalent identification of person(s) authorizing the calibration certificate;

7.4.10.18 Where relevant, a statement to the effect that the results relate only to the items calibrated;

7.4.10.19 Each page of supporting data supplied with the calibration certificate requires identification to ensure the page is recognized as a part of the calibration certificate package;

7.4.10.20 A clearly identified end of the calibration certificate package must be provided.

7.4.11 If the results of calibration as provided by the calibration service providers or reference material data includes reference values or correction factors, the Lab will ensure that spreadsheets used to present data are encoded with the proper formula to account for the correction factor. Any spreadsheet or software used for this will be validated and records will be maintained.

7.4.12 The Analytical Development Manager or Laboratory Management will ensure the device's calibration label has been updated appropriately before making the device available for use. The Analytical Development Manager will update the calibration record and equipment status in the Calibration Database indicating the results of the calibration service.

7.4.13 The Analytical Development Manager resolves any discrepancies discovered during review of the certificate or the calibration label by contacting the calibration service provider, requesting corrective action as appropriate based on the nature of the discrepancy. If the calibration certificate does not include all the information required above, the calibration service provider must provide a valid reason for not including it.

7.4.14 Where equipment performance includes correction factors or reference values, this data is updated and implemented as appropriate based on the outcome of calibration activities to ensure specified requirements are met.

7.5 Problems with Equipment

7.5.1 If calibrated equipment is dropped, damaged, or suspected of being out of calibration, Lab Management or the Analytical Development Manager is notified. If the Analytical Development Manager or Lab Management finds action is required to ensure the equipment meets requirements, the equipment is dispositioned using one or more of the following options:

7.5.1.1 Recalibration or verification

7.5.1.2 Withdrawing the equipment from use

7.5.1.3 Changing the frequency of calibration or verification

7.5.1.4 Limiting the calibrated range or use of the equipment (the equipment is clearly identified as having a limited calibration with the limitation stated on the equipment and in the Calibration Database)

7.5.2 When calibrated equipment is found to be out of calibration, the Analytical Development Manager will assess the validity of previous laboratory activities and the results of previous calibration services performed while the accuracy and precision of the device was in doubt. The Analytical Development Manager will investigate the impact of the potentially errant measurements on laboratory results. The results of the impact investigation are recorded in records associated with the equipment (typically in the Calibration Database).

7.5.2.1 A corrective action to track resolution of the issue may be initiated, as appropriate.

7.5.2.2 When the assessment indicates the accuracy of previous calibration results may have been compromised by calibrated equipment that did not achieve required measurement accuracy and operate with acceptable measurement uncertainty, the Analytical Development Manager or Lab Management will notify affected customers as appropriate in accordance with the nonconforming work routine described in the Nonconformity and Corrective Action procedure QS-108. Records of notification to customer(s) is maintained along with the records described in the Nonconformity and Corrective Action procedure.

7.6 Frequencies and Review for Calibrated Equipment

7.6.1 The Analytical Development Manager reviews the results of each calibration to maintain confidence in the calibration program and calibration status of equipment. This review will consider the amount of usage for the equipment as well as the results of calibration activities. Where a change to the calibration frequency is appropriate, the Analytical Development Manager will edit the calibration frequency indicated in the Calibration Database. A justification for the change, the date of the change and the person authorizing the change (typically the Analytical Development Manager) will also be recorded in the Calibration Database.

7.6.2 Calibration intervals may be shortened or extended based on the following conditions:

7.6.2.1 Where sufficient calibration data exists to statistically establish a trend assuring good measurement results for a period longer than the current period.

7.6.2.2 Limited or extensive use may influence the amount of time between calibrations or verifications, as appropriate.

7.6.2.3 Risk of possible out-of-tolerance drift may also be used as a consideration in adjusting the calibration frequency.

7.6.2.4 Equipment that is delicate, subject to frequent usage or severe conditions (i.e., shock and vibration, excessive heat, or humidity, or transported) is assigned calibration intervals shorter than would be assigned if the equipment were not delicate or subject to frequent use or severe conditions.

7.6.2.5 Infrequently used test equipment (e.g., used once or twice between calibration cycles) may be assigned the status of "Calibrate Before Use" instead of a periodic calibration.

7.6.3 If intermediate checks are necessary to maintain confidence in the calibration status of the equipment, the method and required check frequency is identified in the Calibration Database. Lab Management or Lab Technician will conduct such checks when appropriate based on stated requirements in the Calibration Database. Records of intermediate checks are included in calibration records. If the results indicate an out of tolerance condition exists, an impact investigation is conducted in accordance with the process described above.

7.7 Equipment Maintenance (for equipment not subject to calibration)

7.7.1 Lab Management or the Analytical Development Manager will review the Calibration Database on a routine basis to determine equipment due for maintenance. When the Calibration Database indicates maintenance is required, arrangements are made for maintenance to be performed.

7.7.2 The Equipment Maintenance worksheet in the Calibration Database establishes the control necessary to monitor equipment requiring routine maintenance and/or qualification. The worksheet identifies completed activities, frequency, and due dates.

7.7.3 Scheduled maintenance and operational checks are performed on equipment required for the correct performance of laboratory activities and that can influence calibration results. Required maintenance activities and frequencies

are defined in the Calibration Database. The following is considered when determining maintenance frequency.

7.7.3.1 Manufacturer's recommendation;

7.7.3.2 Amount of use;

7.7.3.3 Risk of equipment failure;

7.7.3.4 Lead time required for repair or replacement of equipment or components.

7.7.4 When equipment breaks down or fails, it is repaired or replaced at the discretion of Lab Management or the Analytical Development Manager. Any repairs or new equipment is ordered and fulfilled according to the Purchasing and Receiving procedure. Records of repairs are maintained in the equipment record.

7.7.5 Equipment that has been subjected to overloading or mishandling, gives suspect results, or has been shown to be defective or outside specified limits, is taken out of service. Such equipment is isolated and/or clearly labeled as being out of service to prevent its use until it has been repaired and has been demonstrated to perform correctly.

7.7.6 Where suspect equipment has been used, Lab Management or the Analytical Development Manager will examine the effect of the defect or departure from specified limits on previous results. Lab Management or the Analytical Development Manager will maintain a record of the investigation in the associated equipment records. Lab Management or the Analytical Development Manager will notify customers as appropriate if previous results have been impacted in accordance with the nonconforming work routine described in the Nonconformity and Corrective Action procedure QS-108. Records of notification to customer(s) are maintained along with the records described in the Nonconformity and Corrective Action procedure.

7.7.7 Maintenance is performed by external services or by internal personnel as determined by Laboratory Management or the Analytical Development Manager. External service providers will conduct maintenance activities as required by contracts or purchasing information provided to the external provider, referencing maintenance or operations manuals, as appropriate. Maintenance performed by internal personnel is conducted according to general maintenance practices and/or in accordance with equipment manufacturer's

recommendation. Records of maintenance activities are maintained as described in C-502 Record Storage, Retention, and Destruction.

8.0 Process Outputs

8.1 Outputs from the Calibration and Equipment Control process include, but are not limited to:

8.1.1 Operational, monitoring, and measuring equipment that performs as required and is calibrated to appropriate standards.

8.1.2 Non-measurement equipment that performs as required.

8.1.3 Records of calibration and maintenance.

9.0 Revision History

Revision	Date	Description of Changes	CCR #	By
0	11/10/21	New procedure.	N/A	J. Maignan