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1.0 Purpose

This SOP describes the equipment calibration program within the Biopharmaceutical Development Program (BDP).

2.0 Scope

This SOP applies to the calibration of CGMP and non-CGMP control, weighing, measuring, monitoring, and test equipment within the BDP, unless otherwise exempted by QA Engineering. This SOP applies to subcontractors and internal personnel who perform calibration services for the BDP. Instructions for how to calibrate specific devices are found in supporting Standard Operating Procedures (SOP).

3.0 Authority and Responsibility

3.1 The Director, Biopharmaceutical Quality Assurance (BQA) has the authority to define this procedure.

3.2 Facilities, Maintenance, and Engineering (FME) is responsible for:

3.2.1 Performing calibration, unless otherwise performed by BDP, or a BDP or FME subcontractor.

3.2.2 Documenting raw calibration data, any adjustments made to the units under test, and applicable comments and/or observations in the calibration program management software.

3.2.3 Notifying at a minimum the Quality Engineering and Validation Manager via email or via means of the calibration software of any out-of-tolerance events identified during calibration. Additional staff such as the Equipment Owner and the Facility Manager would also benefit from the notification. Notification should occur before close of business on the day detected whenever possible.

3.3 Quality Engineering and Validation, BQA is responsible for (Functions with an asterisk* may also be performed by validation contractors of the BDP):

3.3.1 Overseeing the execution of this procedure. *Validation contractors may oversee the performance of calibration by an outside contractor.

3.3.2 Reviewing the Request for Equipment Calibration, Form 21508-01 The Quality Engineer is responsible for ensuring that pertinent information about the equipment is reasonable and customary for its intended use, such as range, tolerance, interval, et cetera.

3.3.3 *Reviewing equipment calibration records.

3.3.4 Performing investigations and assisting the Manager/Supervisor and Project Scientist in determining the potential product impact of equipment which is found to be out-of-calibration.

3.3.5 *Ensuring correct performance and documentation of calibration.

3.3.6 Initiating an Engineering Event (EE) per ***SOP 21526 - Engineering Event Management*** for any out-of-tolerance events requiring an EE.

3.3.7 Determining acceptability of proposed repair/parts replacement strategies when required to correct an out-of-calibration or failure condition, in collaboration with BDP Business Operations, equipment owners, and BDP engineering, as appropriate. Ensuring the appropriate corrective and preventative actions (CAPA) have been properly made, documented, and approved.

3.4 Equipment Owners are responsible for:

3.4.1 Ensuring their equipment is entered into the Calibration Program (see Section 5.1 - Entering Equipment into the Calibration Program).

3.4.2 Submitting or preparing equipment/instruments for calibration on schedule.

3.4.3 Units that are beyond their calibration Due Date are considered **Out of Calibration** as defined in Section 4.1.1. It is the responsibility of the equipment owner to placard these units as “out of service” using Form 21508-03 or posting the equivalent information. CGMP and GLP equipment and instruments beyond their calibration expiry may not be used without an approved deviation, initiated per ***SOP 21301 - Deviations from Written Documents and Corrective and Preventative Actions.***

3.4.4 Ensuring their equipment **IS NOT USED OUTSIDE OF THE CALIBRATED RANGE AND TOLERANCE**.

3.4.5 Determining the root cause and potential impact on production, testing, or R&D activities for equipment which is found to be out-of-calibration, in consultation with the Project Scientist and Quality Engineer.

3.4.6 Notifying BQA or designee if they wish to change the calibration status of equipment, i.e., make the equipment "Inactive," modify the tolerance, etc. Consider changing the Calibration Status to "Inactive" if the equipment will not be used for a long period, as in the case of campaign specific equipment. Approval must be given by BQA or designee before tolerances may be modified. This is best done if the unit has not been used since the last calibration or following a calibration so that there is less risk from as found data OOT. (The calibration software provides an audit trail of all changes.)

3.5 Quality Assurance is responsible for:

3.5.1 Maintaining the calibration section of the Master Equipment Files (MEF).

3.6 BDP Engineering is responsible for:

3.6.1 Informing equipment owners of equipment past due for calibration and pending calibrations each month, providing notice in advance of the due date.

3.6.2 Completing and submitting the Request for Vendor Services form indicating "units to be calibrated according to BDP procedure." (See Attachment 2).

3.6.3 BDP Engineering or a designee enters external vendor calibration data into the software and performs the first review.

3.7 Backup of the database is managed by the IT Operations Group (ITOG) with a routine backup protocol in place. See ***SOP 10102 - Computer System Operations Backup and Recovery*** for additional details.

4.0 Definitions

4.1 **Calibration** – The process of comparing measurement and test equipment to standards of known accuracy to detect and/or rectify deviations.

4.1.1 **Out-of-Calibration –** The state of measurement or test equipment that is either Out-Of-Tolerance (OOT) (see below), or that has exceeded its calibration interval. **(Requests for Vendor Service that pull the equipment from service and are being processed and shipped are not considered to have exceeded the calibration interval as this process sometimes has duration of several weeks for turnaround.)**

4.1.2 **Out-Of-Tolerance (OOT) –** The state of measurement or test equipment that fails to meet its specified level of calibration **(calibrated range and/or calibrated tolerance). Note that this level of calibration may differ from the manufacturer's calibration. Failure to meet the manufacturer's calibration may therefore not create an OOT**. This OOT state must be investigated and documented within the calibration software or as an Engineering Event (EE) if

there is any potential for system or product impact. EEs are tracked according to ***SOP 21526 - Engineering Event Management.***

4.2 **Range -** The smallest and the largest values associated with operation of an instrument.

4.2.1 Manufacturer's Range: The range that is specified by the manufacturer of the unit at the time of sale, over which the Manufacturer's Tolerance (see below) applies.

4.2.2 Calibration Range: The range over which the unit is calibrated, which may differ, by being reduced, from the range over which the unit will operate. The calibration range is set by the equipment owner and Quality Engineering keeping in mind the intended process where the device will be used.

4.3 **Span** – The number of units between the low and high value of the range. For example, a pressure gauge with a calibration range from 20 to 100 psig has a span of 80 psig.

4.4 **Tolerance** - The allowable deviation from a known measurement value, based on the accuracy of the unit under test. A pressure gauge which reads at 100 ± 1 psig has a tolerance of ± 1 psig, or ± 1% (99 to 101 psig). This is also known as the statement of accuracy.

4.4.1 Manufacturer's Tolerance: The statement of accuracy that is guaranteed by the manufacturer of the unit at the time of sale.

4.4.2 Calibration Tolerance: The statement of accuracy that is applied to the unit by the equipment owner and the Quality Engineer. This number reflects the accuracy established for calibration. The calibration tolerance may be wider than the manufacturer's tolerance. The value may never be tighter than the manufacturer's tolerance.

4.4.3 Process Tolerance: This number reflects the accuracy required for the process in which the unit operates. The process tolerance is typically wider than the manufacturer's tolerance and is often wider than the calibration tolerance. The value may never be tighter than the manufacturer's tolerance. Exceeding the process tolerance has the potential to impact the process.

4.5 **Levels of Calibration**

4.5.1 Calibrated (Calibration LEVEL 1): When measurement and test equipment have been compared to primary or secondary standards to detect and/or adjust deviations to within the manufacturer's specifications for tolerance over the full manufacturer's range.

Units that are CALIBRATED LEVEL 1 meet manufacturer's range and manufacturer's tolerance specifications.

4.5.2 Limited Range Calibration (Calibration LEVEL 2): When measurement and test equipment have been compared to primary or secondary standards to detect and/or adjust deviations to within the manufacturer's tolerance specifications over a limited range, which is less than the range specified by the manufacturer. Use is only valid within the stated range.

Units that are CALIBRATION LEVEL 2 do not match manufacturer's range but do match manufacturer's tolerance specifications.

4.5.3 Modified Tolerance Calibration (Calibration LEVEL 3): When measurement and test equipment have been compared to primary or secondary standards to detect and/or adjust deviations to within stated specifications and tolerances as established by BDP and not the manufacturer. Use is only valid within the stated range and tolerance.

Units that are MODIFIED TOLERANCE CALIBRATION LEVEL 3 do not match manufacturer's range and/or tolerance specifications.

4.5.4 Single-point Calibration (Calibration LEVEL 4): When measurement and test equipment have been compared to primary or secondary standards to detect and/or adjust deviations to within the stated specifications and tolerances at one specific point. The point at which the device has been calibrated must be the point at which the device will be used. Measurements taken with the device are valid only if they are within ± 5% of the calibrated point or within ± the tolerance BDP specified for the device, whichever is more stringent.

4.5.4.1 This level of calibration is intended for measuring devices that are an integral part of a larger system and cannot, with ease, be used in some other application. It will be employed when other levels of calibration are not feasible because of concerns for safety of product, equipment, or personnel. The technician must cause a small fluctuation in the reading to ensure that the device under calibration is not stuck in position.

4.5.5 Verified (Calibration LEVEL 5): When a non-calibratable signal is tested for its on/off (binary) characteristic, it is labeled as verification for calibration records.

4.5.6 For Reference Only (Calibration Not Required): This status is applied to instruments that are qualitative indicators only. It also applies to instruments whose output results in no action except directing the user to another CALIBRATED instrument for additional information. Typically, the BDP applies a "For Reference Only" (or FRO) status to instruments with qualitative readouts such as color zone (red/yellow/green) indicators on pneumatic filters or where redundant instruments that are not used for control or process decisions are found. These FRO instruments may also be found on "Indirect Impact" or "No Impact" Systems as defined by ISPE's Pharmaceutical Engineering Guides for New and Renovated Facilities, as well as those utility systems and equipment designated as lowest risk level according to the FMEA-based risk assessment as described in the BDP's Facility Validation Master Plan.

4.6 **Interval**: The period between calibrations of measurement and test equipment.

4.7 **Measurement and Test Equipment**: Instruments or devices used to measure, gauge, test, inspect, or otherwise examine.

4.8 **Primary Measurement Standard**: An instrument or device of known accuracy which is used in a calibration system as a standard of reference and is directly traceable to the National Institute of Standards and Technology (NIST) or equivalent institution.

4.9 **Secondary Measurement Standard**: An instrument or device of known accuracy which is used in a calibration system as a standard of reference and is traceable through other standards to the NIST or equivalent institution.

4.10 **Intrinsic Standard**: A standard of reference by whose construction causes it to follow natural and physical laws of nature. The accuracy of the standard is controlled by the natural and physical laws of nature. Examples include the freezing and boiling points of purified water at standard sea level pressure.

4.11 **Test Accuracy Ratio (TAR)**: The ratio of the tolerance of the unit under test (UUT) to the tolerance of the standard being used for calibration. BDP requires that the TAR be greater than or equal to 4:1. See Section 9.4.

4.12 **Accuracy of Scales and Balances**: Calculate the overall accuracy for a scale or balance, unless specified by the manufacturer, using the NIST Handbook 44, 2000, Section 2.20, Scales, T.N.3. Tolerance Values, Table 6, Maintenance Tolerances, Table 3.

4.13 **As Found**: The condition of an instrument/equipment prior to having an adjustment made to it. This also pertains to the data taken from this instrument/equipment.

4.14 **As Left**: The final condition or condition of an instrument/equipment after having an adjustment made to it. This also pertains to the data taken from this instrument/ equipment.

4.15 **Multichannel Instrument:** A unit that has either separate physical or logical pathways for measurement; for example, multichannel pipettes (separate physical pathways), or airborne particle counters that give results by particle size (separate logical pathways).

5.0 Procedure

5.1 Entering Equipment into the Calibration Program

5.1.1 Purchase Requests (PRs) will be routed through Quality Engineering (QE) and/or FME before new equipment is ordered. QE and/or FME indicates in writing on the PR or via e-mail whether calibration, validation, and other considerations for this equipment are required upon arrival.

5.1.2 BDP Purchasing provides a copy of this PR to the equipment requestor.

5.1.3 When the equipment arrives on-site, if QE has indicated that calibration is required for that piece of equipment, the Equipment Owner completes Form 21508-01, Request for Equipment Calibration.

5.1.4 The Equipment Owner routes the form to BQA Engineering for review and approval.

5.1.5 BDP Engineering or authorized designees enter the information into the calibration software system.

5.1.6 If equipment comes with a Calibration Certificate, the Equipment Owner forwards the certificate to BQA Engineering for review.

5.1.6.1 If BQAE approves the certificate, the calibration due date for the equipment is entered as the date of calibration on the approved certificate plus the calibration frequency (to the end of the month).

If BQAE does not approve the certificate or if equipment does not come with a Calibration Certificate, the initial calibration due date for the equipment will be the day the equipment is entered into the calibration management program.

5.1.7 The approved Request for Calibration is filed in the MEF folder for that piece of equipment.

NOTE: Some equipment may not be acquired via PR and some equipment may have calibration requirements entered directly in the calibration management software without Form 21508-01. Direct entry occurred for many components during relocation to the ATRF. Direct entry is not intended to replace the need for an owner or user to provide and receive consultation on calibration requirements.

5.2 Maintaining a Calibrated Status

5.2.1 BDP Engineering accesses the computer database at least monthly to identify equipment coming due for calibration, as well as overdue calibration dates. This report, which includes Contact Name and Due Date, is distributed to equipment owners monthly. This ensures that equipment owners have advanced notice that their equipment is due for calibration.

5.2.2 The Instrument Shop technician contacts the equipment owner or designee to coordinate a schedule for calibration.

5.2.3 In the event that the calibration is performed by an outside vendor, BDP Engineering completes a “Request for Vendor Services Form,” or RVS, and submits it to the FNLCR Purchasing Department. FNLCR Purchasing attaches a cover letter indicating that the calibration must be completed to meet BDP specifications. A sample cover letter to accompany an RVS Form is given in **Attachment 2**.

5.2.4 In the event that an instrument has exceeded its calibration interval, the instrument is now “Out of Calibration,” as defined in Section 4.1.1. Once notified of or detecting the condition, equipment owners are responsible for placarding the instrument as “Out-of-Service” and handling these units according to Section 3.4. QA will verify that required placarding is in place.

NOTE: The user or equipment owner is also responsible for informing QE or BDP Engineering in writing (e-mail is acceptable) if an instrument is *suspected* to be out of calibration for any reason. Upon notification, QE,

its designee, or the owner will remove the instrument from service using Form 21508-03, until the problem is resolved.

5.3 Changing the Calibration Status

5.3.1 The Calibration Status, including the level of calibration, may be changed for equipment based on usage and criticality/process tolerance.

5.3.2 Change in the level of calibration which includes changing the calibrated range or tolerance will be considered based on system use and criticality/process tolerance.

5.3.3 Changing the status to “Inactive” should be considered if the equipment will not be used for a long period as in the case of campaign specific equipment. This will reserve program resources although the possibility of failure on as-found data since the last usage and calibration must be considered. The unit must be tagged as “out of service” using Form 21508-03 or otherwise posted with the equivalent information. Removing calibration stickers from inactive equipment is recommended but not required. The Area Clearance process per ***SOP 21104 - Pre-Production Clearance*** will review calibration status prior to any GMP use of equipment.

5.3.4 The status will be changed to “Retired” for equipment no longer in service. This would typically occur for components that are damaged beyond repair, totally removed from service, or for equipment that has been retired from use in the MEF program. Placarding of this status is not required as the component or equipment affected is no longer present in the facility or has been changed to a “For Reference Only” status.

5.4 Performing Calibration (In House)

5.4.1 The Instrument Shop technician calibrates the instrument using the BDP instrument-specific SOP for calibration. Follow guidance in ***SOP 22012 – Significant Figures and Rounding of Numbers*** with calibration data.

5.4.2 When performing a calibration, the instrument should be adjusted whenever the as-found value excessively approaches the calibration tolerance. Failure to readjust the instrument will reduce the safety margin against drift during the next calibration interval. As a guide, the as-left value is recommended to provide for a safety margin ≥30% of the calibration tolerance. For example, if the tolerance is ±10 units, the as left should not exceed ±7 units when possible via adjustment. (If consistent tolerance cannot be achieved over the range of the equipment, target the operating range for the lowest deviation.) In the case that the instrument is not adjustable, it is recommended to indicate this fact in the master record of the calibration software. This can also be noted in an equipment history as a comment.

5.4.3 The technician records all data including the application of an electronic signature in the calibration data management software per ***SOP 21555 - Use and Management of Blue Mountain Regulatory Asset Manager***

5.4.4 The technician must enter the necessary information into the equipment logs according to ***SOP 21531 - Equipment Logs***. For Calibration entries this would include at a minimum; date, time, generic description of calibration activity, and the technician's initials. If the work takes more than one day to complete, at least two entries should be made. The first entry will indicate the start of the task and the second would indicate when the task is completed. If the activities are part of a work order, the WO # should be recorded. Failures or replacements should provide sufficient detail to identify the component(s) involved and the action taken.

5.4.5 Details of how to review and approve calibration data are found in ***SOP 21523 - Calibration Data Review.***

5.5 Performing Calibration (External Vendor)

5.5.1 The request for calibration is initiated with a Request for Vendor Service or RVS.

5.5.2 Either the unit is shipped to the vendor site or the vendor comes on-site depending on the agreement to complete the calibration.

5.5.3 The vendor's Calibration Certificate is scanned and attached to the file in the calibration software and any pertinent information entered. The electronic history is then electronically signed for authorship per ***SOP 21555 - Use and Management of Blue Mountain Regulatory Asset Manager***.

5.5.4 Details of how to review and approve calibration data are found in ***SOP 21523 - Calibration Data Review.***

5.5.5 The hard copy of the certificate, with the MEF ID indicated by writing or highlighting it, is sent to BQA for filing in the MEF.

5.5.6 The hard copy need only be filed in the MEF. There is no need to enter the documentation into the MEF TOC as the details, including a link to the scanned document, are sufficiently captured in the Blue Mountain Software.

5.6 Calibration Specifications

5.6.1 Calibrations require as-found and as-left data to be recorded. The only exception to this is in the case of new equipment or disposable equipment such as timers. If new equipment comes with a Calibration Certificate that has been approved by Quality Engineering that data may suffice as "as-found." Otherwise, if no as-found data is available, the unit is considered Out-of-Tolerance (OOT) as defined in Section 4.0. Timers and flowmeters for the glass vessel Celligen are received and placed into service using the Calibration Certificates. These devices may not receive further calibration when their interval is reached and may simply be retired from service. If any other equipment is desired to be handled this way, written justification and approval of Quality Engineering is required.

5.6.2 There must be at least three measurements taken (preferably five), covering at least 70% of the BDP established calibration range of the device or as otherwise specified.

5.6.3 The preferred calibration points are 10% and 90% of the BDP established calibration range and normal setpoint (mid span if no normal or operational setpoint).

5.6.3.1 For loops containing multiple components, the smallest read-out range will be the basis for the manufacturers' specifications and tolerances.

5.6.3.2 For multichannel devices with separate physical channels (i.e., multichannel pipettes), at least three measurements must be taken per channel.

5.6.3.3 For multichannel devices with separate logical channels (i.e., particle counters), at least one measurement must be taken per channel.

5.6.4 The standard used to calibrate has an accuracy of at least four times better than the accepted accuracy of the unit to be calibrated (see Section 9.4 for additional detail).

5.6.5 Standards are NIST traceable whenever available.

5.6.6 Calibrations will take the system's approach. Whenever possible, the transducer, transmitter, and read-out device will be calibrated together as a loop.

6.0 Equipment Labeling

6.1 Internal Calibration

6.1.1 After calibration, a calibration label is created by running the Cal Label Report in BMRAM. Generating labels this way removes the chance of typographical errors on the label as it is automatically generated from the calibration record which is seen by the calibration technician and reviewed by QA.

Examples are included in **Attachment 1**.

Information Found on Calibration Stickers

Sticker Type (A)	B	C	D	E	F	G
Calibrated	X	X	X	X	X	X
Limited Range Calibrated	X	X	X	X	X	X
Modified Tolerance Calibrated	X	X	X	X	X	X
Single Point Calibrated	X	X	X	X	X	X
Verified	X	X			X	X
For Reference Only						

A) The level or type of calibration

B) The identification number (ID number) of the instrument;

C) Date the instrument is next due;

D) Calibrated Range for instrument;

E) Calibrated Tolerance of the instrument

F) Name of person who calibrated the instrument;

G) Date the instrument was calibrated (MM/DD/YY);

6.1.2 The calibration due date for the equipment is the last day of the month of the established interval. For example, if the calibration date was 6/23/20, and the interval for that instrument is 1 year (12 months), then the calibration due date will be listed as 6/30/20.

6.1.3 The calibration attaches the generated calibration stickers. Stickers must be placed in clear view on the instrument. When calibration is performed, the old sticker must be removed and discarded before attaching the new sticker.

6.1.4 If review of the calibration record finds an error that impacts the calibration sticker, a new sticker will need to be generated once the record is corrected. If the range or tolerance was modified the sticker will need to be generated manually as those values cannot be changed on an open work record.

6.1.5 For on demand calibrations, the due date is not displayed on the sticker. A supplemental sticker to display the due date shall be placed adjacent to the calibration sticker or the date added with permanent ink and initial and dated.

6.2 External Vendor Calibration

6.2.1 Due to vendor variability, stickers from external vendors will vary with the format and type of information included.

6.2.2 Stickers must contain at a minimum the following: ID of the equipment and the calibration date. If the calibration interval is anything other than 1 year (due at end of month calibrated) the date calibration is due must also be included.

6.2.3 If the vendor sticker lacks required information a supplemental calibration sticker may be applied.

6.2.4 Alternatively, a BDP sticker may be applied to equipment calibrated by external vendors. This sticker should indicate “Additional calibration information found in calibration database” or similar wording with the same meaning. This is a result of the variability and reduced information as compared with the internal sticker.

7.0 Transportability Testing

7.1 Equipment in the Calibration Program is either portable or non-portable. The non-portable equipment must be recalibrated each time that it is moved over 10 feet.

7.2 Portable equipment is equipment that is deemed portable by the manufacturer. In most cases, it has wheels or has a carrying case or some indication that the manufacturer meant for it to be moved frequently. Along with this assumption is the understanding that the unit has been tested to ensure that it will maintain its calibration throughout its moves. Transportability testing using Form 21508-02 addresses equipment that is

generally possible to move but may not have appropriate testing by the manufacturer to ensure that it will maintain its calibration after a move.

7.3 Procedure

7.3.1 Calibrate the unit. Record the required data along with the location of the unit under test (UUT).

7.3.1.1 Move the UUT to a new site that would approximate the conditions and move distance that the unit is expected to encounter in a “worst-case” operation. Calibrate the unit. Record the required data along with the location of the unit under test (UUT).

7.3.1.2 Move the UUT a second time. It may go back to the original or to a new site.

7.3.1.3 Calibrate the unit. Record the required data along with the location of the unit under test (UUT).

7.3.1.4 Move the UUT a third time.

7.3.1.5 Calibrate the unit. Record the required data along with the location of the unit under test (UUT).

7.3.1.6 The three moves must be completed in less than the calibration interval.

7.3.2 For the initial calibration the unit should be adjusted to the centerline of the tolerance.

7.3.2.1 For subsequent calibrations, “as-found” data must be within tolerance.

7.3.2.2 No adjustment is allowed after the initial calibration.

7.3.2.3 If the unit fails the “as-found,” then perform an investigation to determine the cause. If it is determined that it was not the fault of the move, then the testing can be repeated in its entirety.

7.3.2.4 To be deemed portable for calibration purposes, the UUT must pass calibration each time after a move for three consecutive times.

7.3.3 The testing must be documented.

7.3.3.1 A final report must be written by BDP staff reviewing the data and stating the outcome of the testing.

7.3.3.2 The final report is approved by the Quality Engineer and stored in the calibration file of the Master Equipment Files.

8.0 Unscheduled Recalibration

8.1 Calibrated equipment will be assessed for recalibration after repair, damage, or physical, electronic, or other changes that could impact operation, range, accuracy, or tolerance.

8.2 Any repair that causes the instrument case to be opened may be reason for recalibration of the equipment.

8.3 Any repair that deals with that section of the instrument that affects the parameters being calibrated will be reason for recalibration.

8.4 The equipment owner and BQA Engineering will decide if the date of recalibration may become the calibration date and the start of the new calibration cycle. By system default, the due date will not change with an on-demand calibration event.

8.5 The BDP Engineer, the Equipment Owner, or the BQA Engineer can require recalibration.

8.6 The calibration program will indicate that the reason for calibration was unscheduled and why. The comments shall state whether the unit was repaired or changed.

9.0 Standards

9.1 Standards must always be maintained in a calibrated state or labeled as “Out of Calibration - Do Not Use.”

9.2 Standards must be kept in a clean, secured, low-traffic area when not in use.

9.3 The calibrating agency will have records directly traceable to the NIST.

9.4 Standards must be, at a minimum, four times more accurate than the instrument or device with which they are being compared (4:1), whenever possible. If the standard used for calibration is not at least four times more accurate than the instrument or device, this must be noted on the history for internal calibrations and on the certificate for external calibrations. State the test accuracy ratio (TAR) of the standard to the instrument or device. The 4:1 TAR shall be maintained for internal calibrations unless the BDP does not have an available standard to achieve the required TAR.

9.5 If a standard is found to be out-of-calibration, the investigation shall include a review of all instrumentation calibrated in the past interval using this standard, to determine possible impact.

9.6 Intrinsic standards do not require calibration. However, as all standards must be approved in order to be used per BRRAM, they shall be treated like other standards with respect to history records and review.

10.0 Management of Out-of-Calibration Conditions

10.1 An Out-of-Calibration condition (OOC) occurs when quantitative equipment fails to meet its specified level of calibration (has been found out-of-tolerance or OOT) or has exceeded its calibration interval.

10.1.1 When an OOC is the result of an out-of-tolerance (OOT) condition, encountered during the “as-found” testing, it is recorded, and every effort is made to rectify the situation. How the situation was rectified is recorded by the calibration technician if the method goes beyond calibration adjustment considered standard for the device. If the OOT condition cannot be rectified, the calibration technician removes the equipment from service and attaches an “out-of-service” tag or Form 21508-03 to it and the calibration “Fails.” The calibration technician then notifies, at a minimum the Quality Engineering and Validation Manager, of any out-of-tolerance events identified during calibration. Additional staff such as

the Equipment Owner and the Facility Manager would also benefit from the notification. (This function may be handled via e-mail or automated notification.) Notification should occur before close of business on the day detected whenever possible.

10.1.2 OOT Investigation

10.1.2.1 Each OOT must be investigated. The investigation intent is to determine the impact of the event to the operation of the equipment and any direct or indirect impact to product. In addition, the investigation looks at cause if known, history of the component during previous calibration cycles, and determines if the calibration interval should be reduced or the calibration tolerance widened if allowable based on the process.

10.1.2.2 Investigations are documented in one of two ways; directly within fields in the calibration management software when there is no risk of product impact as supported by the nature of the OOT or facts of the investigation, or via an Engineering Event per ***SOP 21526 - Engineering Event Management***, when there is a possibility of product impact, and should consider other factors such as criticality and the need for additional input from other BDP staff. Examples are provided later in this section; when unclear which method to use, document the investigation using an EE.

10.1.2.3 In the case of an OOT standard, the first step is to perform a reverse traceability report to determine where the standard was used. This report should be included in the investigation whenever results are returned. If the standard was not used during the interval in question, simply state that fact.

10.1.2.4 Example 1. Temperature standard X is found OOT at two points (300°C and 500°C) across the range of 0-500°C. A reverse traceability shows that all components calibrated had a max temperature in their range of 200°C. The calibration points of 0°, 100°, and 200°C met calibration tolerance. It is clear that the failures above 200°C do not impact the calibrations performed. This investigation may be documented without an EE.

NOTE: If the range required is not clearly bracketed i.e., the calibration point of 100°C and the next of 300°C which failed was used you cannot ascertain that things were OK at 200°C. The degree of failure must now be considered in the investigation.

10.1.2.5 Example 2. Pressure standard X has a calibration tolerance of ±0.002 psi and has an OOT with a result of 0.005 psi. As standards should maintain a 4:1 ration unless otherwise stated the OOT difference of 0.003 x 4 = 0.012 psi. If the calibration tolerance of the Unit Under Test (UUT) is not less than 0.012 the calibration is still valid. If the ratio is followed there is no impact, if the ratio is not met there may be impact and an EE should be initiated.

10.1.2.6 Example 3. An analog pressure gauge on an autoclave has failed and as found data cannot be obtained. This calibration would be both OOT and FAIL. The investigation shows that the gauge measures chamber pressure. This failure is not critical in this case if the chamber pressure transducer calibration has met specification. The gauge is non-controlling. The transducer is the instrument that is more accurate and controlling for steps in the autoclave cycle. An EE would not be required.

NOTE: An OOT discovered and reported by calibration services vendor may not be OOT according to BDP specifications. Calibration vendors are required to calibrate BDP instruments according to manufacturers' specifications. If BDP uses a modified tolerance or range (i.e., "process" tolerance or range), and the instrument's calibration data meet those specifications captured for the equipment in the calibration software application, this situation is not considered an OOT. The BDP Quality Engineer who reviews the data from the vendor is responsible for determining whether an OOT per BDP specifications has occurred.

10.2 Equipment that has been removed from its place of operation to be calibrated must not return to that place in an OOC condition. If the article cannot be repaired, it must be given to QA Engineering or BDP Engineering for disposition.

11.0 Documentation

11.1 Calibration is captured in an electronic system via ***SOP 21555 - Use and Management of Blue Mountain Regulatory Asset Manager***.

11.2 Calibration activities must be recorded in the equipment log, when applicable. Refer to Section 5.4.4.

11.3 The calibration section of the MEF contains hard copies of calibration records performed by outside vendors and is maintained by BQA Documentation and kept in accordance with ***SOP 21520 – Equipment Management and Control.***

12.0 References and Related Documents

SOP 10102 *Computer System Operations Backup and Recovery*

SOP 21104 *Pre-Production Clearance*

SOP 21301 *Deviations from Written Documents and Corrective and Preventative Actions*

SOP 21520 *Equipment Management and Control*

SOP 21523 *Calibration Data Review*

SOP 21526 *Engineering Event Management*

SOP 21531 *Equipment Logs*

SOP 21555 *Use and Management of Blue Mountain Regulatory Asset Manager*

SOP 22012 *Significant Figures and Rounding of Numbers*

Form 21508-01 Request for Equipment Calibration

Form 21508-02 Transportability

Form 21508-03 Out of Service

Regulatory References

- **21 CFR 211 Subpart D – Equipment**

  Section 211.68 Automatic, mechanical, and electronic equipment.

a) "Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained."

- **21 CFR 211 Subpart I – Laboratory Controls**

  Section 211.160 General requirements.

b) (b) (4) "Laboratory controls shall include The calibration of instruments, apparatus, gauges, and recording devises at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting the established specifications shall not be used."

- **21 CFR 58 Subpart D – Equipment**

  Section 58.63 Maintenance and calibration of equipment.

c) (a) "Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated, and/or standardized."

d) (b) "The written standard operating procedures required under 58.81 (b) (11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation."

e) (c) "Written records shall be maintained of all inspection, maintenance, testing, calibrating, and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of non-routine repairs performed on equipment because of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect."

- **Guidance for Industry: CGMP for Phase 1 Investigational Drugs, July 2008**

f) Section (V) (C.), Facility and Equipment, states that "Each facility shall provide the following described work area and equipment: Appropriate equipment that will not contaminate the phase 1 investigational drug or otherwise react with, add to, or be absorbed by the phase 1 investigational drug; and that is properly maintained, calibrated, cleaned, and sanitized at appropriate intervals following written procedures."

- **Technical References**

BDP Facility Validation Master Plan, VMP-003.

13.0 Attachments

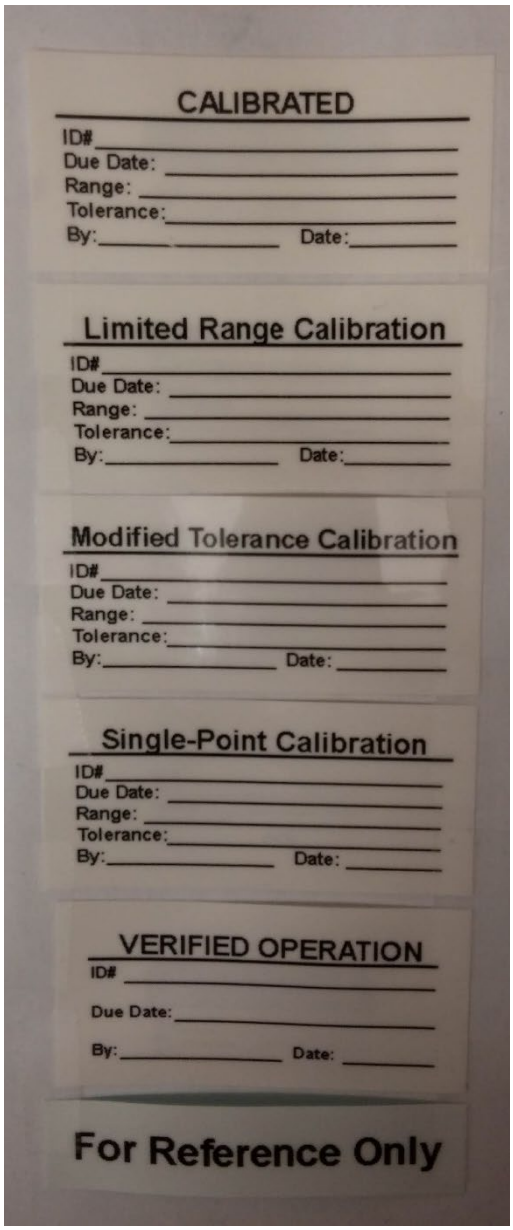
13.1 **Attachment 1** Calibration Stickers

13.2 **Attachment 2** Requirements for Requesting Vendor Calibration

[redacted]

Attachment 1

Calibration Stickers



Attachment 2

Request for Vendor Services Sample Cover Letter

To Whom It May Concern:

The equipment that you are about to calibrate is for the BIOPHARMACEUTICAL DEVELOPMENT PROGRAM (BDP) – Leidos Biomedical Research, Inc. All calibrations must be in accordance with ANSI/NCSL Z540.3 - 2006 or equivalent. These calibrations must have, as a minimum, three (3) data points that cover at least 70% of the range of the unit under test (UUT). The preferred calibration points are 10% and 90%, and normal setpoint (mid span if no normal setpoint). Multi-channel devices with separate *physical* channels (i.e., multi-channel pipettes) must have at least 3 measurements taken per channel. Multi-channel devices with separate *logical* channels (i.e., particle counters) must have at least one measurement taken per channel.

Both the “as received/as found” and “as returned/as left” data must be recorded on the Calibration Certificate by the person(s) performing the calibration procedure(s). Repairs must be authorized before being performed and shall use like-for-like components whenever possible. The description of the repair shall be included on the Calibration Certificate. The Calibration Certificate must be signed by a responsible person within the organization. If the received unit is inoperable, a written statement to that effect must accompany the Calibration Certificate. The “as returned/as left” data can be the same as the “as received/as found” data if no adjustments were made to the UUT.

Standards must be, at a minimum, four times more accurate than the instrument or device with which they are being compared, whenever possible. If the standard used for calibration is not at least four times more accurate than the instrument or device, the test accuracy ratio (TAR) of the standard to the instrument or device must be noted on the calibration datasheet/certificate. Standards shall be NIST-traceable, whenever possible.