- This guidance applies to all GMP sites where chemical or physical testing of Test Articles intended for commercial distribution is performed.

- This guidance applies to test results generated during chemical or physical testing of test articles intended for commercial distribution. The scope includes only those tests for which a Regulatory Specification (RS) and/or a regulatory stability Protocol exists. Production Materials are included within this scope if they have regulatory specification. This guidance does not apply to materials tested by biological methods, results generated during instrument set-up, standardization or suitability or to Test Method Validation.

- Detection of an OOS or Questionable Result shall prompt a review by the Lab Supervisor of the relevant laboratory records.

- If obvious errors are not found that explain the OOS or Questionable Result, or if obvious errors are found that require generation of new, valid data, an Analytical Laboratory Investigation (LI) is initiated using a Laboratory Investigation Report (LIR) Form. The LIR is designed to document all findings and conclusions.

- The laboratory must establish a log and numbering system for LIRs.

- The initial investigation phase of the LI and the Investigational Measurements Protocol (IMP) are performed to determine if an Assignable Cause (AC) (e.g., a Laboratory Error or sampling error) exists that could have caused the OOS or Questionable Result.

- A Retest Protocol may be prepared if no assignable cause is established following both an Initial Investigation and the execution of an IMP. A retest protocol is used to determine if the original OOS or Questionable Result is valid and representative of the Batch/Lot. However, the OOS or Questionable Result may be accepted as valid following the Initial Investigation with no further testing.

- All Original and Retest Results must be documented in the LIR, forwarded to the Quality Assurance (QA) Manager and considered in batch/lot release decisions.

- An Evaluation of the Potential Impact on other samples analysed during the initial testing must also be performed when an assignable cause is found. All test results within the affected run must be assessed for validity. An evaluation of the potential impact on samples that were tested at other times, which may have been affected by the assignable cause, shall also be performed.

  The investigation shall extend to other materials or products that may have been associated with the specific failure or discrepancy.

- The Site Quality Review Team shall be informed by the Site Quality Authority of any of the following events that may result in a potential Market Action:

- All sample tests that were invalidated by establishment of an assignable cause are repeated. The result will replace the original invalidated results only. The original sample preparation(s) shall be used for this testing if the assignable cause was not due to the sample preparation and if the sample preparations are stable.

  A single analysis is performed to replace a single initial OOS or Questionable Result. (For example: An assignable cause has been identified for one of the ten results from a Content Uniformity test or one of the six results from a dissolution test. The original single result is invalidated. To replace the single invalidated result, test one additional dosage unit for the content uniformity test or perform a dissolution test using one dosage unit.) LIR Form Section "Repeat/Retest Protocol" and Section "Repeat/Retest Results" shall be used to document the Repeat Tests and the results obtained.

- An evaluation of the potential impact on other samples analysed during the original testing must also be performed. All test results within the affected run must be assessed for validity. This may be accomplished through the analysis of a Control Sample.

- An evaluation of the potential impact on samples tested at other times that may have been affected by the assignable cause that was found shall be performed.

Retesting (No Assignable Cause Identified):

- A Retest Protocol is prepared.

- LIR Form Section "Repeat/Retest Protocol" shall be approved by the Lab Supervisor prior to any retesting.

- The Retest Protocol must be based on the specific problem identified, the history of the product, method and batch/lot and must delineate the number of retests to be performed.

- Where sample is available, the retest protocol must be executed using the same sample set that was the source of the original OOS or Questionable Result. The retest protocol may include testing on the same composite sample preparation that was the source of the original result, if available, unless there is scientific rationale for not using the same composite sample. The rationale must be documented.

  For instance, if an aliquot of a composite grind from a solid sample has one or more OOS or questionable results, testing of the original tablet grind may be included in the retest protocol.

- Upon completion of the LI for initial OOS results, the Site Quality Authority shall inform the Site Quality Review Team of the outcome of the investigation. The Site Quality Review Team shall determine if issuance of any reports to the relevant Regulatory Authorities is required. This would include an update to any filed initial NDA-Field Alert Reports. .

- In the event of a confirmed OOS result, it may be necessary to issue an alert report to other departments within the site to notify them of the situation. The QA Manager shall ensure that such reports are issued within one business day following confirmation of an OOS result.

  The QA Manager shall also evaluate the need for an investigation into the source of the confirmed OOS result and ensure that any necessary investigations are completed.

Closing the Laboratory Investigation:

- LIR Form Section "Overall Conclusions" and if relevant, Section "Corrective Action Plan" are completed by the Lab Supervisor. Corrective actions as a result of LIRs shall be tracked and documented evidence of these activities shall be available.

- The completed LIR shall be approved by the Lab Manager and the QA Manager, using LIR Form Section "Laboratory Investigation Report Approval".

- All LIRs must be completed and fully approved within twenty (20) business days of the discovery of the initial OOS or Questionable Result. If the laboratory investigation will go beyond twenty (20) business days, an interim status report must be issued to the QA Manager containing, at least, the following:

  - The date of discovery of the OOS or Questionable Result,
  - Reference to the LIR general information,
  - Reason for the delay,
  - Current status of the investigation, and
  - Estimated date for completion of the LIR.

- The Approved LIR shall be archived by the Quality Authority.

- The Approved LIR shall be distributed as per Site procedures.

- LIRs shall be reviewed, at least, once per year to determine if trends are observed that require further corrective action.

Report No: _____

Additional Concerns or Unusual Occurrences:
Section III - Findings / Conclusions of Review:
Section IV - Conclusion Summary and Approval of Initial Investigation:
☐ **Readily Apparent Assignable Cause** ☐ **No Readily Apparent Assignable Cause Found**

☐ **Sample**	☐ **Method**	☐ **Analyst error**
☐ **Instr./equip**	☐ **Calc. error**	☐ **Stability trend**
☐ **Other:**		
Explanation:		

2. Foreign Matter Control, Testing and Inspecting of Sterile Products

- This guidance applies to visual inspection and testing for and control of Foreign Matter in Sterile Active Pharmaceutical Ingredients (API) and sterile Drug Products intended for human use, as called for by Compendial requirements and/or the regulatory filing in the product market(s).

- This guidance applies to GMP Production Sites and operations responsible for performing visual inspections and testing for and control of Foreign Matter in sterile APIs and sterile drug products intended for human use.

- Manufacture of Sterile APIs and Sterile Drug Products shall include controls that minimize the introduction of foreign matter.

- Parenteral drug product solutions in clear Containers shall be 100 percent inspected for foreign matter visually and/or by a Validated automated electronic inspection system.

- Sterile API and sterile drug product batches/lots shall be sampled according to an Approved sampling plan and tested for foreign matter as called for by compendial requirements and/or the regulatory filing for the product market(s).

- Foreign Matter Inspection and Testing shall be performed by Qualified personnel

- Foreign matter test methods (TM) shall be validated for non-compendial test methods and Verified for compendial test methods. All test methods shall be maintained under change control. Automated systems used to perform foreign matter testing and computer-related laboratory systems shall include Validation of the Computerized Systems.

- Test Samples of sterile drug product powder and lyophilized drug products shall be constituted and visually inspected prior to foreign matter testing.

- Designated samples of sterile drug products shall be evaluated for foreign matter by visual inspection, after which they shall be tested for foreign matter using either:

    - Light obscuration testing; or
    - Microscopic particle counting and sizing.

- Laboratory Instruments and Equipment used to perform foreign matter testing shall be Calibrated and/or standardized according to an approved schedule and shall include, and not be limited to:
    - Microscope ocular micrometers, and
    - Light obscuration instruments (e.g., HIAC).

- Sampling and Test Procedures for foreign matter determination shall be written and approved and shall include, and not be limited to:

    - Number of samples to be tested per batch/lot;
    - Amount of each sample to be tested;
    - Test methods;
    - Test equipment; and
    - Retest criteria (e.g., equipment malfunction, sampling error, sample spill) and methods.

- Personnel performing foreign matter testing shall wear a clean, non-shedding garment, powder-free gloves, and clean hair and facial coverings.

- Test samples designated for foreign matter testing shall have the outside of their containers rinsed with filtered (not greater than 0.45 micron filter) Purified Water

- Visual Inspections, using manual inspection methods, for foreign matter in parenteral drug product solutions in clear containers shall be performed as follows:

    - Use inspection stations with illuminated matte black and matte white (BW) backgrounds;

    - Container contents swirled, container inverted and then returned to the upright position, and examined against the black background; and

    - Container contents swirled, container inverted and then returned to the upright position, and examined against the white background.

- Test Samples of sterile powders or lyophilized drug products shall be visually inspected for foreign matter in the laboratory as follows:

    - The product shall be constituted or reconstituted according to a written procedure that shall specify the diluent to be used. Measures shall be taken to (PW) or equivalent water prior to test preparation. Foreign matter test samples shall be prepared in a horizontal HEPA filtered unidirectional airflow environment to ensure that foreign matter is not introduced when the sample is constituted or reconstituted;

    - Container contents swirled, container inverted and then returned to the upright position, and examined against the black background; and

    - Container contents swirled, container inverted and then returned to the upright position, and examined against the white background.

- This guidance applies to the assessment of impurities for release and stability testing of marketed and clinical research Batches and Lots manufactured in GMP facilities and to complaint samples of the following substances:

    - Ophthalmic, injectable, topical, and ingestible human Drug Products;
    - Ophthalmic, injectable, and ingestible animal drug products;
    - Over-The-Counter (OTC) human ingestible products;
    - APIs;
    - Medical Devices; and
    - Reserve Samples tested within their expiration periods.

- This guidance does not apply to the following:
    - Dissolution and Content Uniformity testing;
    - Cleaning verification testing;
    - Topical animal products;
    - Excipients, Raw Materials (RM), In-Process Materials, and Intermediates;
    - Biological or biotechnology products, peptides, oligo-nucleotides, radiopharmaceuticals, fermentation products, semi-synthetic products derived from fermentation, herbal products, and crude products of animal or plant origin;
    - Quality Control Reference Standards qualification;
    - Laboratory Qualification using the Analytical Method Transfer Exercise (AMTE) process; and
    - Test Method Validation Protocols.

- Unidentified Peaks from the Samples shall be evaluated and investigated. Based on scientific judgment, if an unidentified peak is observed in the standard, it can be evaluated per this guidance.

- A Laboratory Investigation (LI) shall be conducted into the source and, if necessary, the identification, of unidentified peaks that exceed applicable Investigation Thresholds. If investigation thresholds are provided in the Test Methods (TM), they shall be applied. If investigation thresholds are not provided in the TM, the thresholds from the International Conference on Harmonization (ICH) guidance shall be followed.

- The Presence and Amount of all Confirmed Unidentified Peaks Above the Investigation Threshold must be reported. The evaluation, investigation and reporting of such peaks shall be performed according to this. Reports of unidentified peak occurrences shall be reviewed by the responsible Lab Supervisor to determine if subsequent actions are required.

- The Lab Analyst shall be responsible for the routine evaluation of chromatograms using an expanded scale to enable the signal-to-noise ratio to be determined, and

how the peak was concluded to be the same as that cited in the original LIR (e.g., by RRT agreement).

- When Completing the Investigational Measurements Portion of the LIR, it is not necessary to complete all steps if one of the steps leads to a conclusion of the investigation. Investigational Measurement steps of an LIR may be completed in any order.

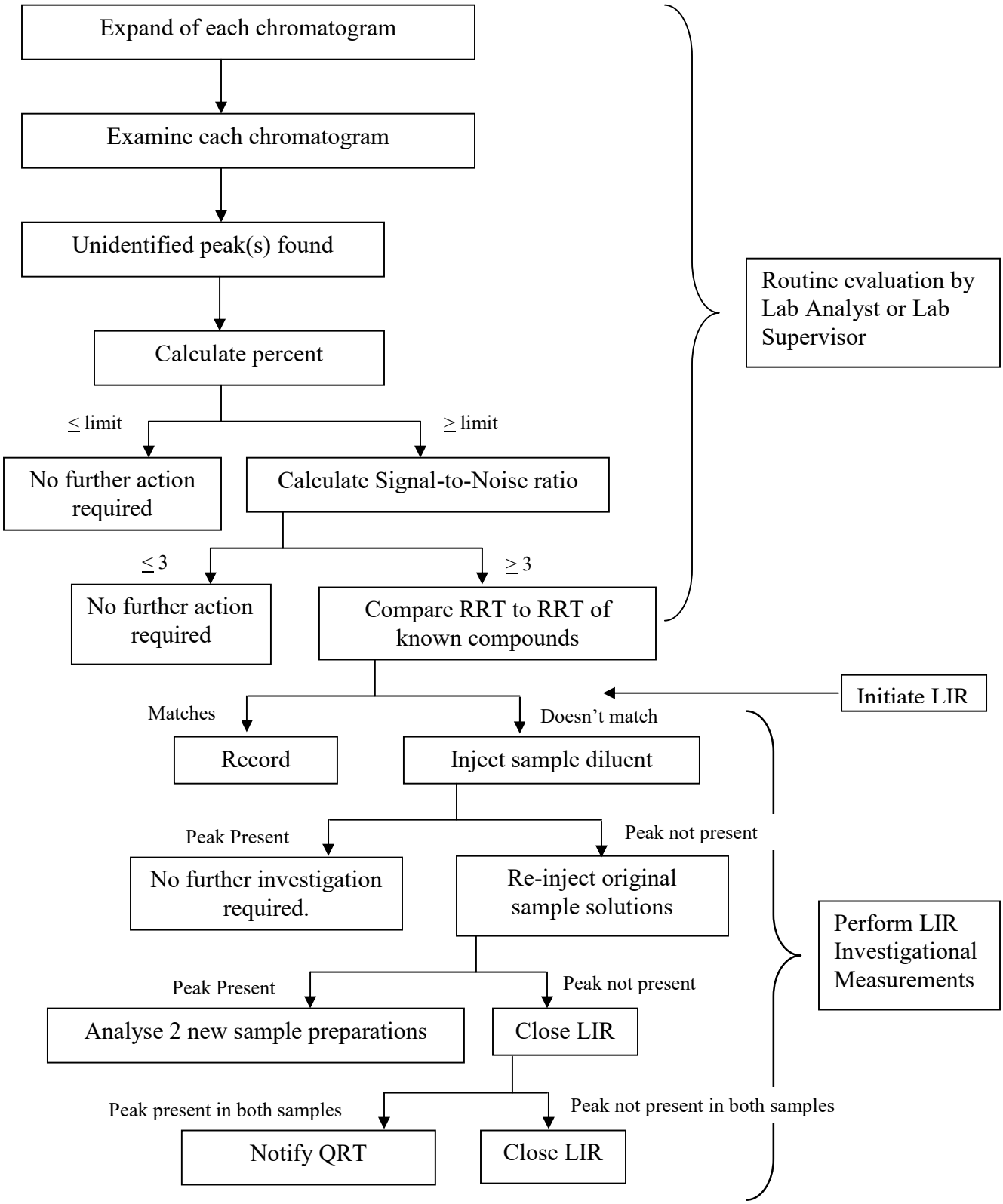
- To Determine if the Unidentified Peak is an Artifact, information from the chromatographic sequence in which the peak was observed shall be reviewed. The following steps provide example situations to consider in determining if the unidentified peak is an artifact:
    - To confirm that the unidentified peak is not caused by the sample diluent, inject an aliquot of the sample diluent into the chromatographic system. If a diluent blank was included in the original chromatographic sequence, it is not necessary to repeat the diluent injection. The resulting chromatograms shall be examined to determine if the unidentified peak is present in any of the diluent blank injections. If the peak is observed as a result of injecting the sample diluent into the chromatographic system, this peak is concluded to be an Artifact Peak and shall be documented as such in the test record;

    - If the peak cannot be attributed to the sample diluent, additional injections of the original sample shall be performed. These injections are for “Information Only” and are not to be used for quantitation. The unidentified peak shall be confirmed as being present at the same RRT in each chromatogram, including the original chromatograms where the unidentified peak was first observed; or (To Determine if the Unidentified Peak is an Artifact):

    - Ensure that the observed unidentified peak is not due to a component from an earlier injection of sample or standard that has a longer RRT than the length of each chromatographic run. Ensure the system is clean (for example by flushing), and evaluate the column in use. If the peak is not observed in each injection of the sample preparation and is not reproducibly attributable to an earlier injection, the unidentified peak can be attributed to an artifact of the chromatographic system.

- If the Source of the Unidentified Peak was Determined to be an Artifact Peak, the LIR shall be closed. The source of the artifact, if known, shall be documented in the test record and in the LIR. Possible causes of artifact peaks include, and are not limited to, the following:
    - Improperly cleaned glassware;
    - Old or contaminated solvents and Reagents;
    - High Performance Liquid Chromatography (HPLC) column; and
    - Contamination within the HPLC equipment.

Decision Tree for Unidentified Peaks



- Laboratory Water Systems shall be qualified for their intended use. The water system shall be maintained, monitored on a routine basis and must be suitable for use for the specified Test Method (TM) or test material preparation. In addition, the water system in the microbiology laboratory must, at a minimum, meet the quality attributes for Purified Water (PW).

  Non-Compendial Test Methods used for release testing and stability testing shall be validated to the established standard in place when the method was developed. The suitability of all test methods used shall nevertheless be qualified under actual conditions of use and documented.

  Established and previously validated non-compendial methods shall be re-validated to contemporary standards when a regulatory agency requires such re-validation as a condition of filing (e.g., registration recertification, registration amendments, or refiling).

  All test methods shall be maintained under change control. Other methods, such as in-process test methods, shall be validated as specified by approved procedures.

- Personnel Performing Testing and personnel approving test results shall be Qualified.

- Biological, Toxic, and Hazardous Waste Materials shall be handled according to local, regional, and/or national guidelines and Corporate Environmental Health and Safety (EHS) Guidelines.

- A Sample Handling System shall be in place and include provisions for:
  - Sample receipt, proper sample labeling, and sample log-in;
  - Prevention of sample loss, sample mix-ups, and contamination;
  - Verification that information on the sample label matches the accompanying document submission;
  - Identification of potent, toxic or hazardous compounds requiring special precautionary measures;
  - Sample storage at room temperature unless otherwise indicated;
  - Tests performed within a defined time period after sample receipt;
  - Investigation of sample mix-ups or contamination;
  - Sample retention until all tests are completed and there is a determination as to whether a result is valid or invalid; and
  - Sample destruction or disposal.

- Controls for Preventing Cross Contamination shall be available and implemented.

Bulk liquid and semi-solid dosage form products shall be held for no more than five (5) calendar days, unless hold time studies have been conducted or historical data are available that support longer hold times in bulk containers. Hold time studies shorter than five (5) days must be considered for products that are highly susceptible to the influence of the holding conditions (e.g., held under heat, susceptible to separation with time, or susceptible to microbial growth).

- A Stability Program shall be established for APIs to support re-evaluation intervals or expiration dates, when required by regulatory commitments. Re-evaluation Dates assigned to API intermediates for sale must be supported by stability data.

- The First Three (3) Released Batches of Each API shall be placed on the stability monitoring program to confirm the re-evaluation intervals or expiration dates. However, where data from previous studies show that the API is expected to remain stable for at least two (2) years, fewer than three (3) batches can be used, if in accordance with local regulatory requirements (see ICH Q7 – Ref 11).

  Potential need for Accelerated Stability Testing must be evaluated in accordance with local regulatory requirements, at all Sites so affected.

- At Least One Batch per Year of API Manufactured (unless none is produced that year) shall be added to the stability-monitoring program and tested annually to confirm the stability, unless otherwise specified by Regulatory Authorities. Testing protocols for APIs with short re-evaluation dates or expiry periods [less than twenty-four (24) months] shall include more frequent testing up to the re-evaluation date or expiration date. After this date, testing shall be conducted annually for the duration of the study or until Out-Of-Specification (OOS) Results are obtained, whichever occurs sooner.

- Stability Samples from APIs and API Intermediates for Sale shall be stored in containers that simulate the market container. For example, if the API or API Intermediate for Sale is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller scale drums of similar or identical material composition to the market drums.

- Maximum Allowable Hold Times shall be established for APIs that are held in bulk containers for more than thirty (30) calendar days. APIs which are held in bulk containers prior to final packaging [e.g., blender, tote bin or Intermediate bulk container (IBC)] for thirty (30) calendar days or longer shall be retested prior to use, unless hold time studies have been conducted or historical data are available that support longer hold times in bulk containers. Studies for hold times shorter than thirty (30) days must be considered for APIs that are highly susceptible to the influence of the holding conditions (e.g., held under heat, susceptible to separation with time or susceptible to microbial growth).
  Requirements for Consumer Non-Drug Products

- If a Non-Compendial Test Method (TM) or Modified Compendial Method is used, the test must yield results equivalent to or superior to a corresponding compendial test method. The justification to perform the non-compendial or modified test method shall be included in the Final Validation Report.

- All Test Methods (TM), including compendial, modified compendial, and non-compendial, shall be maintained under change control.

- Performance Capability of the Test Laboratory must be demonstrated under actual use conditions before any test method is implemented.

- Validation Protocols and Reports shall be approved by the Site Quality Team.

- Sterility Testing shall be conducted in a Grade A Aseptic Processing Area (APA), a Grade A Air Classification cabinet located within a Grade B APA environment or in a Sterility Test Isolator System (STIS).

- Qualified Personnel and Qualified Test Laboratories shall be used to perform BET and sterility testing. Sterility test results shall be Trended and reviewed, at least, annually by the Laboratory Manager to identify such issues as the occurrence of false positives and the quality of Laboratory Analyst performance.

- Procedures for Sampling and Testing of RMs, APIs, drug products and medical devices shall be written and approved and shall include:
    - Number of samples to be tested per batch/lot;
    - Amount of each sample to be tested;
    - Test methods;
    - Test equipment;
    - Retest criteria and methods; and
    - Test limits.

- BET and Sterility Test Reagents and Microbiological Culture Media shall be purchased from Approved Suppliers. No decisions regarding disposition shall be made about the materials under test until the reagents and culture media used have been approved for use. Purchased media and reagents must meet all requirements defined in this guidance. Additionally, the manufacturer's requirements for storage and Expiration Dating must be met.
- Standard Operating Procedures (SOP) shall describe the preparation, labeling, storage and use of laboratory reagents, volumetric solutions, Reference Standards and microbiological culture media.

- Sterility Test or BET Failures shall be Investigated and the Laboratory Investigation Report (LIR) approved by the Site Quality Team prior to final batch/lot disposition.

- Compendia Specified Microorganisms (as applicable to the product filing market) and at least one well characterized environmental isolate shall be used in Bacteriostasis, Fungistasis, and growth promotion testing.

- Maintenance of Microbiological Control Cultures shall be specified and documented and include, and not be limited to:
    - Verification of culture purity and identification at specified time intervals, but not less than annually unless the culture is stored cryogenically. For cultures stored under cryogenic conditions, viability of the frozen organisms shall be periodically tested at intervals determined by documented risk assessment;

    - Seed lot culture maintenance techniques to ensure that viable microorganisms are not more than (NMT) five (5) passages removed from the original type culture strain; and

    - Culture strains that have been obtained from a recognized reference culture Supplier, such as American Type Culture Collection (ATCC) and National Collection Type Culture (NCTC).

- Bacteriostasis and Fungistasis Testing shall be validated and performed as follows:
    - Conduct three (3) separate studies;
    - Conducted for each test method;
    - Reassessed with any formulation change according to compendial requirements applicable to the product filing market; and
    - Include a growth promotion test as a positive control.

    Where the product or sample exhibits antimicrobial activity, modify the conditions following compendia guidelines (e.g., add antimicrobial inhibitor, modify rinsing) and repeat the stasis test.

- Growth Promotion Testing shall be:
    - Performed on each batch/lot of media;
    - Conducted prior to or concurrently with product sterility testing;
    - Challenged with compendia specified organisms;
    - Inoculated with NMT one hundred (100) cfu and the microorganism population verified by viable plate counts; and
    - Positive for growth by visual in section within three (3) days for bacteria and five (5) days for fungi. Sterility test results obtained using media that is concurrently undergoing growth promotion testing shall not be used for batch/lot release until the media on test has been approved and released.

  - Polypropylene reaction tubes shall never be used.

- BET shall be performed using water free of detectable endotoxins [e.g., Limulus Amebocyte Lysate (LAL) Reagent Water (LRW) or sterile Water for Injection (WFI)].

- The Label Claim Lysate Sensitivity shall be confirmed according to compendial test (as applicable to the product filing market) and include the following:

  - Label claim sensitivity of each new lot of lysate shall be confirmed prior to use or when there is any change in the experimental conditions; and
  - One vial of lysate from each lot shall be tested in quadruplicate.

- Once the Lysate Label Claim is verified, the label claim value shall be used in all future calculations involving that lot.

- The Lysate shall be prepared, used, and stored according to the manufacturer's recommendations.

- A Certificate of Analysis (COA) of the Control Standard Endotoxin (CSE) compared against the Reference Standard Endotoxin (RSE) shall be available and shall be specific for a particular lysate or bacterial endotoxin lot combination. If the required COA is not available or incomplete, a CSE to RSE comparison shall be performed, using one vial each of CSE and RSE.

- Validation of a BET Method for the drug product, API, medical device or RM shall include:
  - Determination of the Maximum Valid Dilution (MVD);
  - Inhibition and enhancement testing of the material for interfering factors;
  - Test of the material at a dilution less than or equal to the MVD;
  - Test on three (3) batches/lots of material;
  - Positive [i.e., material spiked at two (2) times the lysate sensitivity] and negative controls; and
  - Evaluation of the types of glassware/plastic ware and associated equipment and materials on BET results.

- Inhibition and Enhancement Testing shall be conducted for each material according to compendial requirements (as applicable to the product filing market) to demonstrate that the material does not inhibit or enhance the reaction or otherwise interfere with the test as follows:
  - Tests shall be performed on, at least, three (3) Production batches of each finished material;
  - Negative controls shall be included; and
  - If the material shows inhibition, the material may be diluted, not to exceed the MVD or neutralized and the test repeated.

reaction times of the replicates of each standard before performing Regression-Correlation Analysis);
  - Ensure that the coefficient of correlation, "r", is greater than or equal to 0.980. If "r" is less than 0.980 the cause of the non-linearity shall be determined and the test repeated; and
  - Qualification of laboratory personnel by successfully completing three (3) independent assays.

- Qualification of the Laboratory and Personnel to Perform BET by Gel-Clot shall include, and not be limited to:
  - Testing one vial of lysate in quadruplicate;
  - Diluting the RSE and CSE to bracket the lysate label claim sensitivity (i.e., 2λ, λ, 0.5λ, and 0.25λ); and
  - Verifying the label claim of the geometric mean of the end points confirm the lysate label claim sensitivity by +/-one two-fold dilution.

- Each Analyst that Performs BET shall be qualified initially by performing lysate label claim sensitivity. Periodic re-qualification shall be performed annually, unless the analyst has been continually and successfully performing lysate label claim sensitivity and documented as a part of the analyst's training records.

8. Sterility Test Isolators

- Sterility Test Isolator Systems (STIS), that are used to perform sterility testing of Sterile Raw Materials (RM), Active Pharmaceutical Ingredients (API), Medical Devices and Drug Products, shall be designed and operated in a manner that precludes the ingress of microorganisms.

- This guidance applies to GLP laboratories using sterility test isolator systems to perform sterility testing of sterile raw materials, Components, Intermediates, APIs, In-Process Materials, drug products, Biologics and sterile medical devices for Pharmaceutical and Animal Health.

- STIS Configurations shall be classified as follows:
  - Stand alone workstation isolators, and
  - Workstation isolators having one or more transfer isolators.

- STIS Surface Sterilization shall be Validated, requalified and routinely performed on a basis defined at the Site.

- Validation of the STIS shall include provisions for Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), change control, Revalidation, requalification and maintenance. Validation and requalification of

- Exterior Surfaces of Test Sample Containers and Supplies shall be surface sterilized prior to initiating sterility testing by loading the items into a non-surface sterilized STIS workstation (for the stand alone units) or transfer isolator and surface sterilizing the workstation or transfer isolator and exterior surfaces of the items simultaneously. Occluded surfaces shall be wiped with a surface sterilant equal to the efficacy of the sterilant, which is used during routine surface sterilization. Occluded surfaces may include:

    - Test supplies,
    - Test samples, and
    - Isolator components (e.g., half suits).

- Special Requirements for preparation of samples prior to placing them in either the transfer or workstation isolator shall be addressed in written and approved SOPs.

- Acceptance Criteria for STIS Microorganism Monitoring shall be no detectable contamination. An Environmental Monitoring Report (EMR) shall be issued and an Investigation conducted for all positive monitoring samples recovered from isolators.

- Point of Use Microbial Retentive Filters shall be used with compressed gases, and connections, valves and control instrumentation shall be free of Dead-Legs that cannot be sanitized.

9. Transfer of Analytical Methods

- The Purpose of guidance is to establish a documented process for the transfer of analytical methodology. This guidance shall also be used for microbiological and/or bioanalytical method transfer.

- This guidance applies to GLP laboratories responsible for transferring or receiving methods for analysis of therapeutic products including the methods transfer for New Products originating from different GMP sites.

- The process described in this guidance applies to the Analytical Method Transfer Exercise (AMTE) to be followed for analytical methods used in the testing of Active Pharmaceutical Ingredients (API), Drug Products and Medical Devices and may be used for the transfer of Approved methods for analysis of regulatory Starting Materials, isolated Intermediates and Raw Materials (RM), as applicable.

- When contract or non-Site laboratories are involved in an analytical method transfer, the site participants involved shall determine the transfer strategy to be followed.

from other flasks. If sample or standard solutions are transferred to vials, each vial shall have a unique identifying mark to distinguish it from other vials.

- The Date of First Opening of a reagent or reference standard shall be recorded on the label or included on the container in a permanent manner. The identification of the person opening the container shall also be included. If it is not practical to include the date of first opening on the container (i.e., due to extreme storage conditions or limited label space) the date shall be recorded on the associated documentation. If a Validated Computerized System is available for tracking the date of opening, it is considered equivalent to manually recording.

- Storage of Reagents and Reference Standards and their preparations, shall be according to label directions, SOPs or other documentation describing the storage practice.

- Storage Time Periods and Conditions shall be defined in a site SOP for purchased and prepared reagents and reference standards if not defined elsewhere.

- A Notification System shall be established at each site to ensure lab personnel are aware and informed of what the current standard is, and of any information relating to the change in status of a reference standard, including discontinuance of standards.

11. Verification of Compendial Analytical Methodology

- This guidance defines the requirements for the Verification of newly implemented Analytical Methodology from Compendia [including but not limited to, United States Pharmacopeia (USP), European Pharmacopoeia (EP), Japanese Pharmacopoeia (JP), British Pharmacopoeia (BP) and Food Chemical Codex (FCC)].

- This guidance does not address:
  - Verification of microbiological or bioanalytical methods; or
  - Test Methods (TM) associated with Equipment Cleaning Validation.
  - Compendial monitoring for changes to compendial methods.
  - Analytical Methods Validation.

- This guidance applies to analytical methods included in compendia and which are used for release or stability evaluation of Active Pharmaceutical Ingredients (API) and finished Drug Products in or intended for the market place.

- Compendial Methods shall be verified to demonstrate that a validated compendial method can be applied to an API or drug product and yield acceptable results under typical test conditions of use (e.g., equipment, personnel, and Reagents).

- Laboratory personnel to perform the verification studies using the compendial method;
- The Lab Manager responsible for the verification studies is responsible for assuring analytical methods are verified according to this guidance and for reviewing and approving the verification protocol and report; and
- The Quality Team, independent of the Lab Manager, is responsible for reviewing and approving the Method Verification Report for compliance with applicable Site policies and procedures.

- The Need for and Degree of Re-Verification shall be determined by the Lab Manager. Changes for which re-verification shall be considered include, but are not limited to:
  - Changes to the compendial method (e.g., new or modified sample preparation procedure, change to separation or detection conditions, change to instrument settings and/or operating conditions);
  - Changes to the sample being tested (e.g., process change for API or change in formulation of the product); or
  - Changes in compendial or regulatory requirements.

- If a Compendial Method Fails to Meet the Acceptance Criteria for verification, an Investigation must be conducted and documented according to the site Standard Operating Procedure (SOP). If an Assignable Cause for the method failure is identified, corrective action(s) shall be implemented and the verification study repeated.

13. Microbiology Laboratory Investigations
(Refer to Page 11 for Laboratory Investigation (LI) Process Flowchart)

- Upon Discovery of any OOS or Questionable Result and before initiating any investigational measurement, repeat testing or retesting, the Lab Analyst shall immediately, take the following actions:
  - Report the results to the Lab Supervisor;
  - Document findings;
  - Document obvious errors (e.g., spilling of solutions o incomplete transfer of sample or standard), if known;
  - If possible, retain all original samples and test preparations, such as sample solutions, standard solutions, glassware, Microbiological Culture Media and Reagents used in the analysis and subsequent Investigation until the Initial Investigation is completed. Samples shall be retained in a manner that ensures their integrity (e.g., refrigerated).

isolates from the sterility test failure added to the product to determine if the isolate(s) can survive in the product. Such testing shall be considered as investigative to invalidate the data.

- Upon Completion of the IMP Exercise, the Lab Supervisor completes LIR Section VI "Findings/Conclusions from Investigational Measurements and Alert Evaluation":
    - If Assignable Cause is Clearly Identified as a result of the IMP exercise, the initial OOS result is invalidated. The original testing is repeated to generate valid original results; or
    - If No Assignable Cause is Identified as a result of the investigational measurements, the Lab Manager must evaluate the need for an Alert.
- The Data Generated During the IMP is for investigation only and shall not be used as a valid test result.
- If No Readily Apparent Assignable Cause is Determined by either the Initial Investigation or the IMP, it may be necessary to issue an alert report to notify others of the situation. The Lab Manager shall determine whether an alert report is needed and notify the QA Manager that an alert report is needed. The QA Manager shall ensure that such reports are issued within one business day following the completion of Section IV of the LIR Form or Section VI if an IMP was conducted. The Site Quality Authority shall inform the S-QRT which shall determine if the issuance of any reports to relevant Regulatory Authorities is required. NDA-Field Alert Reports (when required) must be issued within three business days of the initial observation of an OOS result if no readily apparent assignable cause is found. The SQRT is responsible for notifying the A-QRT in the event of any proposed market action (e.g., Product Recall), SDN or NDA-Field Alert Reports.

Repeating the Test (Assignable Cause Identified)

- All Tests That Were Invalidated by establishment of an assignable cause are repeated. The repeat test result(s) shall replace the original invalidated results only. The original sample preparation(s) shall be used for this testing if:
    - There is sufficient quantity of sample remaining to repeat the test;
    - The assignable cause was not due to sample preparation;
    - The sample preparations are stable and maintained under proper environmental conditions; and
    - The sample or the sample preparations are not contaminated.
- LIR Form Section VII "Repeat/Retest Protocol" and Section VIII "Repeat/Retest Results" shall be used to document the repeat tests and the results obtained. The

Evaluation of Results

- If an Assignable Cause is Associated with the Original OOS or Questionable Result, the original result is invalidated and the impact of the assignable cause on other samples in the test must be determined.

- Data From the Original Sample shall be retained in the test record, invalidated and not included in the batch disposition decision when an assignable cause has been established.

- A Sterility Test shall not be repeated, and the lot shall be Rejected, if an assignable cause cannot be attributed to the laboratory for the original OOS.

- If No Assignable Cause is Found to be Associated with the Original OOS, and retesting is performed, all test results shall be documented on the LIR, forwarded to the QA Manager, and considered in batch/lot release decisions.

- If the Test Method is shown by investigation to be in question, a general review of the method must be conducted, and required corrective action taken.

Reporting Results

- Invalidated OOS Results shall not be averaged with repeat test results for reporting purposes.

- LIR Form Section VIII "Repeat/Retest Results" shall be used to report results [i.e., the value determined to be the final valid results (e.g., the repeat results, or the confirmed initial OOS)].

- Upon Completion of the LI for Initial OOS Results, the Site Quality Team shall inform the Site Quality Review Team (SQRT) of the outcome of the Investigation. The SQRT shall determine if issuance of any reports to the relevant Regulatory Authorities is required. This would include an update to any filed initial NDA-Field Alert Reports. The SQRT is responsible to take action in the event of any proposed market action (e.g., product recall), SDN, or initial or follow-up NDA-Field Alert Reports.

- A Confirmed OOS Microbiological Test Result shall result in rejection of the test article, unless an approved reprocessing method is available and can be implemented.

- In the Event of a Confirmed OOS Result, it may be necessary to issue an alert report to other departments within the Site to notify them of the situation. The QA Manager shall ensure that such reports are issued within one business day following confirmation of an OOS Result.

