BIOSPECTRA

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QUALITY MANUAL

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1. INTRODUCTION

1.1. Objective

1.1.1. The objective of this Quality Manual is to detail how BioSpectra, as a manufacturer of Active Pharmaceutical Ingredients, Excipients and Process Chemicals, complies with ICH Q7 Good Manufacturing Practice Guidelines for Active Pharmaceutical Ingredients (API). This document will reference all associated documentation within BioSpectra's Quality System for further evidence of compliance to the regulations, standards and guidelines.

1.2. Regulatory Applicability

1.2.1. BioSpectra's Stroudsburg, PA facility manufactures excipients classified under the Bio Excipient Grade in accordance with the ICH Q7 Good Manufacturing Practice Guide. BioSpectra's Bangor, PA facility manufactures Active Pharmaceutical Ingredients classified as Bio FUISA and Bio Active Grade, and Excipients classified as Bio Excipient Grade in accordance with the ICH Q7 Good Manufacturing Practice Guide.

1.3. Scope

1.3.1. This Quality Manual applies to the manufacture of Active Pharmaceutical Ingredients and Excipients for use in the pharmaceutical industry.

1.3.2. Document titles referenced in this quality manual may be subject to change and can be found in BioSpectra's approved quality management system.

1.3.2.1. The document control numbers for the referenced Document Titles can be found in Appendix A: Quality Management System.

1.3.3. Any document referenced in this manual can be accessed using BioSpectra's approved electronic document management system.

1.3.4. BioSpectra has elected to create the Quality Manual in accordance with ICH Q7 although both ICH Q7 and IPEC Good Manufacturing Practices are followed at each manufacturing facility as applicable to the grade of product produced. This Quality Manual is specific to ICH Q7 as it is the highest level of GMPs implemented at each BioSpectra manufacturing facility listed in 1.2.1.

2. QUALITY MANAGEMENT

2.1. Principles

2.10 Quality should be the responsibility of all persons involved in manufacturing.

Requirement	Description
2.10	BioSpectra has defined the commitment to Quality of all personnel involved in manufacturing within the Company's Quality Policy Statement. "It is our position that only a total commitment to Quality will lead to the Quality Goods that we have come to represent; that Quality cannot be tested into our goods but must be present at the beginning; in the procedures, materials, equipment, and personnel."

2.11 Each manufacturer should establish, document, and implement, an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

Requirement	Description
2.11	BioSpectra has an established Quality System. The Quality Policy - states: "The [Quality] system is designed to create a culture in which our controls, equipment, staff and work environment assure that our products achieve the identity, safety, quality and purity characteristics we represent." Additionally, Leadership Review ensures management involvement and review of all company activities as listed in the Leadership Review document.

2.12 The system for managing quality should encompass the organizational structure, procedures, processes, and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.

Requirement	Description
2.12	The organizational structure of BioSpectra is defined in the Company Organizational Chart. As defined in the Quality Policy Statement, it is the responsibility of BioSpectra to provide adequate procedures, processes, and resources to ensure the integrity of the finished product. All Quality related activities are required to be documented in accordance with good documentation practices as defined in BioSpectra's Documentation Entry and Error Correction procedure.

2.13 There should be a Quality Unit that is independent of production and that fulfills both Quality Assurance (QA) and Quality Control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Requirement	Description
2.13	BioSpectra's Quality Unit fulfills both QA and QC responsibilities and is defined in the BioSpectra Organizational Chart as the Regulated Systems Division and Laboratory Services Division. General expectations of the BioSpectra Quality Unit are defined in the Company's Quality Policy Statement.

2.14 The persons authorized to release intermediates and APIs should be specified.

Requirement	Description
2.14	In accordance with BioSpectra's Quality System, the Quality Assurance Department or qualified designees are responsible for Batch Record review and ultimately batch release. Additional information regarding batch release is located in the Batch Record Review and Approval Procedure.

2.15 All quality related activities should be recorded at the time they are performed.

Requirement	Description
2.15	BioSpectra's Documentation Entry and Error Correction and Data Integrity procedures define that all GMP work performed must be documented as they are executed.

2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

Requirement	Description
2.16	BioSpectra's Discrepancy Investigation procedure ensures deviations from procedures are documented and investigated. Planned deviations from procedures may also be documented and approved using BioSpectra's Temporary Operating Instruction program.

2.17 No materials should be released or used before the satisfactory completion of evaluation by the Quality Unit(s) unless there are appropriate systems in place to allow for such use.

Requirement	Description
2.17	BioSpectra requires a member of Quality Assurance, or qualified designee, to review all batch production records and sign a final disposition statement regarding the release of the batch. Additionally, the status of the material is visible to employees through the validated ERP system and associated Tracker ID label that is placed on the material. Material status will be Approved, Quarantined, or Rejected, as appropriate.

2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions.

Requirement	Description
2.18	BioSpectra's Inspections by Government Regulatory and Environmental Health, Safety, and Security Agencies procedure defines the notification procedures in the event of a regulatory inspection. BioSpectra's Discrepancy Investigation procedure defines the notification and subsequent review procedure of any Good Manufacturing Practice (GMP) deficiencies or product defects.

2.2. Responsibilities of the Quality Unit(s)

2.20 The Quality Unit(s) should be involved in all quality-related matters.

Requirement	Description
2.20	The Quality Policy Statements procedure includes the Quality Unit Statement for quality-related matters. The Quality Unit is involved in all quality-related matters.

2.21 The Quality Unit(s) should review and approve all appropriate quality-related documents.

Requirement	Description
2.21	BioSpectra requires Quality approval on all documentation in accordance with BioSpectra's MasterControl Document Creation Revision Review and Approval Process procedure in BioSpectra's current electronic Document Management System.

2.22 The main responsibilities of the independent Quality Unit(s) should not be delegated. These responsibilities should be described in writing and should include but not be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside of the control of the manufacturing company
2. Establishing a system to release or reject raw materials, intermediates, packaging and labeling materials
3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution
4. Making sure that critical deviations are investigated and resolved
5. Approving all specifications and master production instructions
6. Approving all procedures impacting the quality of intermediates or APIs
7. Making sure that internal audits (self-inspections) are performed
8. Approving intermediate and API contract manufacturers
9. Approving changes that potentially impact intermediate or API quality
10. Reviewing and approving validation protocols and reports
11. Making sure that quality related complaints are investigated and resolved

12. Making sure that effective systems are used for maintained and calibrating critical equipment
13. Making sure that materials are appropriately tested, and the results are reported.
14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and or intermediates where appropriate
15. Performing product quality reviews

Requirement	Description
2.22.1	BioSpectra requires a member of Quality Assurance, or qualified designee, to review all batch production records and sign a final disposition statement regarding the release of the batch in accordance with the Materials Handling and Batch Record Review and Approval Procedures.
2.22.2	BioSpectra's Materials Handling procedure governs the release or rejection of Raw Materials, Intermediates, and Components, including packaging. Labels must be reviewed by the Quality Assurance Department or qualified designee in accordance with the Label Creation, Approval, and Issuance Procedure.
2.22.3	BioSpectra requires a member of Quality Assurance, or qualified designee, to review all batch production records and sign a final disposition statement regarding the release of the batch in accordance with the Materials Handling and Batch Record Review and Approval Procedure. Included in this review is a quality review of all associated laboratory testing, both in-process and release testing.
2.22.4	BioSpectra's Discrepancy Investigation and QC Laboratory Investigation procedures define the review and approval procedure of any critical deviations by the Quality Unit. When a deviation is noted during manufacturing, approval from the quality unit is required to continue manufacturing. Additionally, Quality approval is required for closure of the discrepancy/investigation.
2.22.5	Specifications and master production instructions are controlled through the BioSpectra Document Management System. BioSpectra requires Quality approval on all documentation in accordance with BioSpectra's MasterControl Document Creation Revision Review and Approval Process procedure in BioSpectra's current electronic document management system.

Requirement	Description
2.22.6	BioSpectra requires Quality approval on all documentation in accordance with BioSpectra's MasterControl Document Creation Revision Review and Approval Process procedure in BioSpectra's current electronic document management system.
2.22.7	BioSpectra's Quality Unit is responsible for the Internal Audit Program which is described in the Internal Audit Procedure.
2.22.8	BioSpectra does not currently utilize any intermediate and API contract manufacturers. If required for use, they would be qualified and Change Notification provided in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan and Change Control Procedures.
2.22.9	Quality approval is required for all Change Controls initiated and executed at BioSpectra as indicated in the Change Control procedure.
2.22.10	Quality approval is required for all BioSpectra validation protocols and reports as indicated by the BioSpectra Validation Master Plans.
2.22.11	The Quality Unit is responsible for managing and investigating complaints reported to BioSpectra as indicated in the Written and Verbal Complaints procedure.
2.22.12	The Equipment Preventative procedure requires Quality Assurance personnel review Preventative Maintenance records for any potential impact to product quality. As indicated in the Calibration procedure, it is the responsibility of the Quality Unit to maintain effective systems for calibrating critical equipment.
2.22.13	It is the responsibility of the Laboratory Services Division to ensure that all materials are analyzed, and the results are reported. The designation of this responsibility is present for all Analytical Method documentation. Analytical Method documentation is specific to each product.
2.22.14	Quality Assurance is responsible for assigning batches to BioSpectra's stability program. Batches are assigned to the stability program during validation and one cGMP manufactured lot per year after validation. The Laboratory Services Division is responsible for all stability testing. The Stability Testing Program procedure documents these requirements and responsibilities.
2.22.15	Annual Product Review reports are issued as indicated in the Annual Product Reviews procedure.

2.3. Responsibilities for Production Activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures
2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions
3. Reviewing all Production Batch Records and ensuring that these are completed and signed
4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated, and the conclusions are recorded.
5. Making sure that production facilities are clean and, when appropriate, disinfected
6. Making sure that the necessary calibrations are performed and records kept.
7. Making sure that the premises and equipment are maintained and records kept.
8. Making sure that validation protocols are reviewed and approved
9. Evaluating proposed changes in product, process or equipment
10. Making sure that new and, when appropriate, modified facilities and equipment are qualified

Requirement	Description
2.3.1	Production review is required for all manufacturing documents as they are created and/or modified in accordance with MasterControl Document Creation Revision Review and Approval Process procedure in BioSpectra's current electronic document management system.
2.3.2	All Batch Records describe the responsibilities of trained production personnel on how to manufacture the finished goods in accordance with the pre-approved instructions.
2.3.3	Qualified production personnel are required to review all production Batch Records in accordance with the Batch Record Review and Approval Procedure.
2.3.4	As indicated in the Discrepancy Investigation Procedure, "The Director of Manufacturing, Production Manager, or designee is responsible for investigating any discrepancy involving failure to conform to written procedures in production and/or processing, or when a process discrepancy has been detected during manufacturing or packaging operations."
2.3.5	As indicated in the Equipment Cleaning and Maintenance procedure, Cleaning Worksheet Procedure, and Production Area Cleaning procedure, production is responsible for ensuring that production facilities are clean and when appropriate, disinfected.
2.3.6	The Calibration procedure states "Any inspection, measuring and/or test equipment used for GMP purposes must be calibrated." As described in the respective batch record, production must ensure that necessary calibrations are current before use. Calibration records are kept as described in the Calibration procedure.

Requirement	Description
2.3.7	As indicated in the Equipment Cleaning and Maintenance procedure, Cleaning Worksheet Procedure, and Production Area Cleaning procedure, production is responsible for ensuring that production premises and equipment are maintained and records kept.
2.3.8	All Validation Protocols and Reports are reviewed and approved by the Validation Team including a member of production, where applicable to production.
2.3.9	Production approval is required for Change Controls as indicated in the Change Control procedure.
2.3.10	It is the responsibility of Manufacturing Management to participate in new, and when appropriate, modified facilities and equipment qualifications as indicated in the Equipment Qualification Master Plan.

2.4. Internal Audits

2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

Requirement	Description
2.40	BioSpectra conducts internal audits in accordance with the Internal Audit procedure on a schedule as dictated by the Internal Audit Schedule.

2.41 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

Requirement	Description
2.41	Internal Audit findings are reported to the responsible department manager at the conclusion of each internal audit in accordance with the Internal Audit procedure. Agreed corrective actions are completed in a timely and effective manner. Additionally, Internal Audit findings are discussed as a part of Leadership Review in accordance with the Leadership Review procedure.

2.5. Product Quality Review

2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

1. A review of critical in-process control and critical API test results
2. A review of all batches that failed to meet established specification(s)
3. A review of all critical deviations or non-conformances and related investigations
4. A review of any changes carried out to the processes or analytical methods

5. A review of results of the stability monitoring program.
6. A review of all quality-related returns, complaints and recalls
7. A review of adequacy of corrective actions

Requirement	Description
2.50.1	In-process results, and Critical Quality Attributes (CQAs) are reviewed in the Annual Product Review reports in accordance with the Annual Product Reviews procedure.
2.50.2	All Batch Records with confirmed and unconfirmed out of specifications results are reviewed in the Annual Product Review reports in accordance with the Annual Product Reviews procedure.
2.50.3	All discrepancy investigation reports and QC laboratory investigations are reviewed in the Annual Product Review reports in accordance with the Annual Product Reviews procedure.
2.50.4	All Change Controls, as related to the manufacturing process, analytical methods, as well as document revision changes in analytical methods and Batch Records, are reviewed in the Annual Product Review reports in accordance with the Annual Product Reviews procedure.
2.50.5	Stability Testing Program Results are reviewed in the Annual Product Review reports in accordance with the Annual Product Reviews procedure.
2.50.6	All complaints, returns and recalls are reviewed in the Annual Product Review reports in accordance with the Annual Product Reviews procedure.
2.50.7	A review of adequacy of corrective actions is performed in accordance with the Annual Product Reviews procedure.

2.51 The results of this review should be evaluated, and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

Requirement	Description
2.51	As part of the conclusion for each Annual Product Review, a process rating is derived from the data reviewed using both statistical and practical deductions. Any suggested proactive corrective/preventative actions and risk assessments and recommendations should be discussed if applicable.

3. PERSONNEL

3.1. Personnel Qualifications

3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

Requirement	Description
3.10	BioSpectra Quality Policy statements define the responsibilities of BioSpectra management to provide adequate staffing with the appropriate combination of training, experience and/or education to participate or supervise in the manufacturing of finished product.

3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

Requirement	Description
3.11	The responsibilities of all personnel participating in the manufacturing, supervision and/or approval of the finished good are defined in each quality system procedure and production Batch Record.

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

Requirement	Description
3.12	The training required for each employee is outlined in the Employee Quality GMP Training procedure and Employee Required Safety Training. Additionally, new and revised procedures are assessed at the Training Checkpoint step of the Document Management System Workflow for training assignment in accordance with the MasterControl Training Module Administration SOP. On-the-job training plans are available as appropriate by department. Records of training are maintained in accordance with Record Storage Retention & Control. Training is periodically assessed, as applicable.

3.2. Personnel Hygiene

3.20 Personnel should practice good sanitation and health habits.

Requirement	Description
3.20	BioSpectra's Product Care procedure states "Employees with apparent illness are prohibited from working where direct contact with the product cannot be avoided." Additionally, this procedure states "eating and/or drinking is not permitted in any production area, warehouse or QC lab."

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved, and this clothing should be changed, when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn, when necessary, to protect intermediates and APIs from contamination.

Requirement	Description
3.21	BioSpectra's laboratory, maintenance and production personnel, at minimum, are required to wear company provided uniforms. Additionally, personal protective equipment (PPE), such as hairnets, beard restraints, safety glasses, safety shoes, boot covers, and coveralls, are available for all personnel as job duties require. Specific job PPE requirements can be found in BioSpectra's Product Care procedure and the Gowning Master Plan procedure.

3.22 Personnel should avoid direct contact with intermediates or APIs.

Requirement	Description
3.22	BioSpectra's Product Care procedure states "Employees with apparent illness are prohibited from working where direct contact with the product cannot be avoided."

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

Requirement	Description
3.23	Personnel in the manufacturing areas of BioSpectra are not permitted to eat, drink, smoke, chew, or store food in these areas. This is designated via appropriate signage and specified in BioSpectra's Product Care procedure.

3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

Requirement	Description
3.24	BioSpectra's Product Care procedure states "Employees with apparent illness are prohibited from working where direct contact with the product cannot be avoided."

3.3. Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Requirement	Description
3.30	BioSpectra utilizes the Service Provider Questionnaire to assess the education, training, and experience, or any combination thereof, to evaluate Consultants that may advise on the manufacture and control of Intermediates or APIs.

3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

Requirement	Description
3.31	BioSpectra utilizes the Service Provider Questionnaire to maintain the name, address, qualifications, and type of service provided by the consultants.

4. BUILDINGS AND FACILITIES

4.1. Design and Construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

Requirement	Description
4.10	BioSpectra's facilities have been designed and constructed in a manner, which allows for safe and effective cleaning, as well as the maintenance and operations of equipment used in the manufacture of the finished good in accordance with the Equipment Qualification Master Plan, Equipment Preventative Maintenance and the Equipment Cleaning and Maintenance Procedure. BioSpectra conducts Environmental Monitoring per approved procedures to monitor exposure to objectionable microbiology contaminants.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

Requirement	Description
4.11	BioSpectra's facilities have been designed and constructed in a manner to prevent contamination and mix-ups.

4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

Requirement	Description
4.12	All of BioSpectra's manufacturing equipment is located indoors. If BioSpectra were to have equipment outdoors, it would have adequate protection of the material.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

Requirement	Description
4.13	The flow of materials through BioSpectra's facilities is documented in the Materials Handling procedure. This procedure has been designed to prevent mix-ups and contamination.

4.14 There should be defined areas or other control systems for the following activities:

1. Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection
2. Quarantine before release or rejection of intermediates and APIs.
3. Sampling of intermediates and APIs
4. Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)
5. Storage of released materials
6. Production Operations
7. Packaging and labeling operations
8. Laboratory operations

Requirement	Description
4.14.1	Materials received by BioSpectra are received in accordance with the Materials Handling Procedure. This document accounts for the receipt, identification and quarantine of incoming materials. Materials are sampled in accordance with the Materials Handling Procedure for Components and Sampling Matrix Procedure for Raw Materials.
4.14.2	Quarantine before release or rejection of intermediates and APIs is managed in accordance with the Materials Handling Procedure and validated ERP system.
4.14.3	Sampling of finished goods is performed in accordance with the respective batch record.
4.14.4	Holding of rejected materials before further disposition is performed in accordance with the Materials Handling procedure in an approved BioSpectra location.
4.14.5	Once materials have been approved by the Quality Unit, materials are stored in the warehouse by Shipping and Receiving personnel in accordance with the site-specific Current Warehousing Plan.
4.14.6	All production operation areas are clearly identified and segregated from other areas to prevent contamination.
4.14.7	Packaging and labeling operations are conducted inside the controlled production operation areas when the product is being manufactured or repackaged.
4.14.8	Laboratory operations are conducted within designated laboratory locations at BioSpectra facilities.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air dryers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

Requirement	Description
4.15	BioSpectra provides all employees access to washing and toilet facilities that are separate from, but easily accessible to, manufacturing areas. All washing and toilet facilities are maintained by BioSpectra's Housekeeping Department and are stocked with soap and air dryers and/or single service towels. Additionally, BioSpectra provides facilities for showering and/or changing clothes to all employees.

4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

Requirement	Description
4.16	BioSpectra's laboratory operations are conducted in separate designated laboratory areas. In-process analysis is conducted by production personnel and Laboratory Services personnel inside the designated laboratory area or in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurement and the laboratory and its operations do not adversely affect the production process or finished good.

4.2. Utilities

4.20 All utilities that could have an impact on product quality (e.g. steam, gas, compressed air, heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

Requirement	Description
4.20	All BioSpectra utilities that have the potential to impact production quality are qualified in accordance with BioSpectra's Equipment Qualification Master Plan. Utilities are appropriately monitored through the Equipment Preventative Maintenance program. Drawings of these utilities are available in the individual utility qualifications.

4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

Requirement	Description
4.21	Adequate ventilation, air filtration and exhaust systems are provided for all BioSpectra finished goods, where appropriate. API Suites at BioSpectra have dedicated air handling and heating, ventilation, and air conditioning (HVAC) systems. These systems are designed and maintained in order to prevent cross contamination and contamination of the product. When the finished API is exposed to the environment, BioSpectra utilizes two layers of differential positive pressure and high efficiency particulate air (HEPA) filtration of the air to protect the finished product.

4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

Requirement	Description
4.22	Adequate ventilation, air filtration and exhaust systems are provided for all BioSpectra finished goods, where appropriate, to control risks of contamination and cross-contamination. API Suites at BioSpectra have dedicated air handling systems and HVAC to control risks of contamination and cross-contamination.

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

Requirement	Description
4.23	All BioSpectra permanently installed pipework is clearly labeled with the contents and direction of flow on the pipe work.

4.24 Drains should be of adequate size and should be provided with an air brake or a suitable device to prevent back-siphonage, when appropriate.

Requirement	Description
4.24	Production processes are not equipped with any drains. All waste material is pumped to a waste tote, which is transferred to a waste tank.

4.3. Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

Requirement	Description
4.30	Water used for the manufacturing of Active Pharmaceutical Ingredients and Excipients at BioSpectra's Bangor, PA facility conforms to specifications established by the Unites States Pharmacopeia (USP) and European Pharmacopeia/British Pharmacopeia (EP/BP) USP/EP Purified Water or Water for Injection. Water used for the manufacturing of Excipients at BioSpectra's Stroudsburg, PA facility conforms to specifications established by the Unites States Pharmacopeia (USP) and European Pharmacopeia/British Pharmacopeia (EP/BP) for USP/EP Purified Water. Additional microbiological analysis is conducted in accordance with the site-specific Water Testing Methods procedure.

4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

Requirement	Description
4.31	The BioSpectra Purified Water System Performance Qualifications met guidelines for potable water quality as established by the World Health Organization Drinking Water Regulations.

4.32 If drinking (potable) water is insufficient to assure API quality and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

Requirement	Description
4.32	Water used for the manufacturing of Active Pharmaceutical Ingredients and Excipients at BioSpectra conforms to specifications established by USP and EP/BP for Water for Injection and/or Purified Water in accordance with the respective BioSpectra's facility qualification. Additional microbiological analysis is conducted in accordance with the site-specific Water Testing Methods.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

Requirement	Description
4.33	Water used for the manufacturing of Active Pharmaceutical Ingredients and Excipients at BioSpectra conforms to specifications established by USP and EP/BP for Water for Injection and/or Purified Water in accordance with the respective BioSpectra's facility qualification. Additional microbiological analysis is conducted in accordance with the site-specific Water Testing Methods. The USP/EP Purified Water Systems and Water for Injection System have been validated at BioSpectra.

4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

Requirement	Description
4.34	Water used for the manufacturing of Active Pharmaceutical Ingredients and Excipients at BioSpectra conforms to specifications established by USP and EP/BP for Water for Injection and/or Purified Water in accordance with the respective BioSpectra's facility qualification. Additional microbiological analysis is conducted in accordance with the site-specific Water Testing Methods. The USP/EP Purified Water Systems and Water for Injection System have been validated at BioSpectra.

4.4. Containment

4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillin or cephalosporins.

Requirement	Description
4.40	BioSpectra does not manufacture any highly sensitizing materials.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

Requirement	Description
4.41	BioSpectra does not manufacture any material of an infectious nature or materials which have high pharmacological activity or toxicity involved.

4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel and materials moving from one dedicated area to another.

Requirement	Description
4.42	BioSpectra utilizes several different precautionary measures to prevent cross-contamination from personnel or materials when moving from one dedicated area to another. BioSpectra's Gowning Master Plan and Product Care procedures ensure that personnel handle product and themselves in a manner that prevents cross-contamination of product. Additionally, as detailed in the API Master Production Records, positive air pressure differentials are used to protect the product from contamination and cross-contamination. Dedicated air handlers and HVAC systems are also used for the production of Active Pharmaceutical Ingredients.

4.43 Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

Requirement	Description
4.43	BioSpectra does not manufacture any material of an infectious nature or materials which have high pharmacological activity or toxicity is involved.

4.5. Lighting

4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

Requirement	Description
4.50	BioSpectra ensures through Housekeeping and Preventative Maintenance programs that the facility maintains adequate lighting levels.

4.6. Sewage and Refuse

4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

Requirement	Description
4.60	Production processes are not equipped with any drains. All waste material is pumped to a satellite waste tote, which is transferred to a waste tank. Waste products are handled in accordance with the Waste Handling procedure.

4.7. Sanitation and Maintenance

4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

Requirement	Description
4.70	BioSpectra maintains the buildings utilized to manufacture in accordance with the Production Area Cleaning procedure, Warehouse Area Cleaning procedure, and Facility Housekeeping procedure. The Housekeeping Department ensures general facility cleanliness.

4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

Requirement	Description
4.71	BioSpectra assigns the responsibility for sanitation and has procedures to be used in cleaning buildings and facilities. These include, for example, the Production Area Cleaning procedure, Warehouse Area Cleaning procedure, and Facility Housekeeping procedure. Production equipment is cleaned in accordance with the Process Cleaning Validation Master Plan and Cleaning Worksheet Procedure. The Housekeeping Department ensures general facility cleanliness.

4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.

Requirement	Description
4.72	BioSpectra has procedures for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents, as applicable. Production equipment is cleaned or sanitized in accordance with the Process Cleaning Validation Master Plan and Cleaning Worksheet Procedure. BioSpectra maintains the buildings utilized to manufacture in accordance with the Production Area Cleaning procedure, Warehouse Area Cleaning procedure, and Facility Housekeeping procedure. The Pest Control procedure governs the usage of any suitable pest prevention materials.

5. PROCESS EQUIPMENT

5.1. Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitation (where appropriate), and maintenance.

Requirement	Description
5.10	BioSpectra qualifies equipment utilized in the manufacturing of finished goods to provide evidence that the equipment is suitable for its intended use and of appropriate design and adequate size in accordance with the Equipment Qualification Master Plan. The Equipment Qualification Master Plan also establishes the preventative maintenance plan for the equipment. Additionally, Production equipment is cleaned or sanitized in accordance with the Process Cleaning Validation Master Plan and Cleaning Worksheet Procedure.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

Requirement	Description
5.11	BioSpectra performs leaching studies on all new process equipment and the intended materials of construction to be used in the new process to ensure that the manufactured product will not adversely interact with the materials of construction. This study is performed in accordance with the Leaching Study procedure.

5.12 Production equipment should only be used within its qualified operating range.

Requirement	Description
5.12	BioSpectra establishes qualified operating ranges in accordance with the Equipment Qualification Master Plan. Process qualifications and validations are conducted within these operating ranges.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

Requirement	Description
5.13	All major manufacturing equipment is identified through an Equipment Identification Number in accordance with the site-specific Process Equipment Identification procedure.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter the quality of APIs or intermediates beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects on the material's fitness for use. Wherever possible, food grade lubricants and oils should be used.

Requirement	Description
5.14	Utilization of substances associated with the operation of equipment is clearly defined in the specified equipment qualification in accordance with the Equipment Qualification Master Plan. Additionally, lubricants and oils utilized by BioSpectra are food grade, whenever possible.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

Requirement	Description
5.15	Closed or contained equipment is used whenever possible. When this is not possible, additional environmental controls, such as positive air differentials or precautionary procedural controls, are implemented to minimize risk of contamination. Additionally, the Product Care procedure provide guidelines to all BioSpectra employees, visitors and Service contract providers regarding protecting BioSpectra products from contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

Requirement	Description
5.16	All BioSpectra equipment that have the potential to impact product quality are qualified in accordance with BioSpectra's Equipment Qualification Master Plan. Equipment is appropriately monitored through the Equipment Preventative Maintenance program. Piping and Instrumentation Diagram drawings (P&ID) of equipment are available in the supporting documentation associated with the specific Qualification Documentation.

5.2. Equipment Maintenance and Cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

Requirement	Description
5.20	Schedules and procedures are established, including the designation of responsibilities for equipment in accordance with the Equipment Preventative Maintenance program.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

1. Assignment of responsibility for cleaning of equipment
2. Cleaning schedules, including, where appropriate, sanitizing schedules.
3. A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment
4. When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning
5. Instructions for the removal or obliteration of previous batch identification.
6. Instructions for the protection of clean equipment from contamination prior to use
7. Inspection of equipment for cleanliness immediately before use, if practical
8. Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate

Requirement	Description
5.21.1	The assignment of responsibility for cleaning of equipment is defined in both the Process Cleaning Validation protocols and Cleaning procedures.
5.21.2	Cleaning and Sanitizing Schedules, where applicable, are in accordance with the product specific batch record requirements and Cleaning Worksheet Procedure.
5.21.3	Specific process suite cleaning procedures and the Cleaning Worksheet Procedure include a complete description of the methods and materials, including dilution of cleaning agents, when applicable, that are used to clean equipment.
5.21.4	Specific process suite cleaning procedures contain instructions for assembly and disassembly of any required equipment to ensure proper cleaning.
5.21.5	BioSpectra identifies lot numbers via Equipment Cleaning and Use Logs that are continued documentation regarding the current status of the equipment. Additionally, equipment is identified utilizing Production Identification Tags. Tags are removed in accordance with the procedure.
5.21.6	BioSpectra protects cleaned equipment in accordance with the Equipment Cleaning and Maintenance procedure.
5.21.7	Equipment is inspected by production before use in order to ensure that equipment is suitable for use in accordance with the Pre-Process Room Inspection procedure.
5.21.8	The maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate, is in the product specific batch record. Dirty Hold Time and Clean Hold Time Requirements are detailed in the Equipment Cleaning and Maintenance procedure.

5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

Requirement	Description
5.22	Equipment and utensils are cleaned and stored for each Active Pharmaceutical Ingredient and Excipient in accordance with the Cleaning Worksheet Procedure and Equipment Cleaning and Maintenance procedure.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

Requirement	Description
5.23	BioSpectra conducts periodic cleaning in accordance with the production batch record and Cleaning Worksheet Procedure to ensure that that build-up and carry-over of contaminants is not occurring in accordance with the Process Cleaning Validation Master Plan.

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

Requirement	Description
5.24	All non-dedicated equipment is cleaned in accordance with BioSpectra's production batch record and Cleaning Worksheet Procedure between production of different materials to prevent cross contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

Requirement	Description
5.25	Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents is defined and justified in accordance with the Process Cleaning Validation Master Plan and site-specific Cleaning Reference Sheet.

5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

Requirement	Description
5.26	All BioSpectra manufacturing equipment is identified through the use of production identification tags in accordance with the Production Identification Tags procedure. The production identification tags display the equipment identification number and the status of cleanliness of the equipment, as well as the contents if applicable.

5.3. Calibration

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

Requirement	Description
5.30	Controlling, weighing, measuring, monitoring and testing equipment is calibrated in accordance with procedures and schedules as established in the Calibration procedure.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.

Requirement	Description
5.31	All standards utilized in the calibration of BioSpectra equipment are traceable to certified standards where appropriate as defined in BioSpectra's Calibration procedure.

5.32 Records of these calibrations should be maintained.

Requirement	Description
5.32	Calibration records are maintained in accordance with the Calibration procedure and the Record Storage Retention and Control procedure.

5.33 The current calibration status of critical equipment should be known and verifiable.

Requirement	Description
5.33	The current calibration status is displayed on the equipment through calibration stickers in accordance with the Calibration procedure.

5.34 Instruments that do not meet calibration criteria should not be used.

Requirement	Description
5.34	Instruments that do not meet calibration criteria are tagged "Do Not Use"in accordance with the Calibration procedure.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

Requirement	Description
5.35	Critical instruments that fail to meet calibration criteria require an associated Discrepancy Investigation to determine the potential impact to the API or Excipient in accordance with the Calibration procedure and the Discrepancy Investigation procedure.

5.4. Computerized Systems

5.40 GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.

Requirement	Description
5.40	GMP related computerized systems are validated in accordance with the Computer System Validation Master Plan to determine the depth and scope requirements of the validation.

5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

Requirement	Description
5.41	Installation and operational qualifications are conducted to demonstrate suitability of computer hardware and software in accordance with the Computer System Validation Master Plan.

5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

Requirement	Description
5.42	Commercially available software with a cGMP impact is assessed and validated in accordance with the Computer System Validation Master Plan, where appropriate.

5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

Requirement	Description
5.43	Where applicable, computerized systems have been validated to demonstrate compliance with 21 CFR Part 11 to prevent unauthorized access or changes to data. The Data Integrity Procedure details these requirements.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

Requirement	Description
5.44	Written procedures are available for the operation and maintenance of computerized systems for each GMP computerized system utilized by BioSpectra.

5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

Requirement	Description
5.45	BioSpectra's computerized systems that have input of critical data are verified by a secondary person.

5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

Requirement	Description
5.46	Incidents that are related to computerized systems would be investigated through the Discrepancy Investigation procedure, respective computerized system incident procedure, or Supplier Corrective Action Request process.

5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

Requirement	Description
5.47	Changes to computerized systems are managed through BioSpectra's Change Control procedure.

5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

Requirement	Description
5.48	All BioSpectra systems are backed up on a regularly scheduled frequency to prevent information loss as stated in the Information Technology Security procedure. Data protection is established for all computerized systems in accordance with the Information Technology Security procedure and Computer System Validation Master Plan.

5.49 Data can be recorded by a second means in addition to the computer system.

Requirement	Description
5.49	BioSpectra's systems allow for a secondary means of data input into a computer system, such that data is transcribed and verified by a secondary person from hard copies of written data on approved protocols, Batch Records, and Laboratory Notebooks, where applicable.

6. DOCUMENTATION AND RECORDS

6.1. Documentation Systems and Specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

Requirement	Description
6.10	BioSpectra prepares, reviews, approves and distributes documents related to the manufacture of Active Pharmaceutical Ingredients and Excipients in accordance with BioSpectra's MasterControl Document Creation Revision Review and Approval Process procedure in BioSpectra's current electronic document management system.

6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

Requirement	Description
6.11	Revision histories are created for all BioSpectra documents and track the issuance, revision, superseding and withdrawal of documents in accordance with BioSpectra's MasterControl Document Creation Revision Review and Approval Process procedure in BioSpectra's current electronic document management system.

6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

Requirement	Description
6.12	The retention period for all documents is defined in the Record Storage, Retention and Control procedure.

6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

Requirement	Description
6.13	The retention period for all documents is defined in the Record Storage, Retention and Control procedure. Batch Records have a minimum retention period of 6 years from date of approval to ensure at least 1 year after the expiration of the batch, or 3 years have passed after distribution of the last lot of the product if there is no expiration date available.

6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.

Requirement	Description
6.14	When corrections are required for BioSpectra documentation, corrections are made in accordance with the Documentation Entry and Error Correction procedure. All corrections made to entries are dated and initialed (signature equivalent). The original entry remains legible. All entries are made in indelible black ink.

6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

Requirement	Description
6.15	BioSpectra documentation from any facility is readily available.

6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies, such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

Requirement	Description
6.16	BioSpectra documentation is retained in its original format and as a scanned electronic copy, where applicable, in accordance with Record Storage, Retention and Control and the Document Control Library Procedure.

6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically affect quality. Acceptance criteria should be established and documented for in-process controls.

Requirement	Description
6.17	Specifications are established and documented for all raw materials, APIs, Excipients, components, and labeling and packaging materials. Specifications for processing aids, gaskets and other such materials are documented in the Installation Qualification procedure for the equipment. Specifications are established and documented for in-process controls.

6.18 If electronic signatures are used on documents, they should be authenticated and secure.

Requirement	Description
6.18	Electronic signatures are in accordance with 21 CFR Part 11 and the Documentation Entry and Error Correction procedure, where applicable.

6.2. Equipment Cleaning and Use Records

6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

Requirement	Description
6.20	BioSpectra documents the use, cleaning and maintenance of the major equipment utilized to manufacture Active Pharmaceutical Ingredients and Excipients in accordance with the Equipment Cleaning and Maintenance procedure and Equipment Preventative Maintenance procedure. This documentation includes the date, time (if appropriate), product and batch number of each batch processed in the equipment and the person who performed the cleaning and maintenance.

6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

Requirement	Description
6.21	Records of cleaning, maintenance and use of equipment are found in process room specific Equipment Cleaning and Use Logbooks.

6.3. Records of Raw Materials, Intermediates, API Labeling and Packaging Materials

6.30 Records should be maintained including:

1. The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt
2. The results of any test or examination performed and the conclusions derived from this
3. Records tracing the use of materials
4. Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications
5. The final decision regarding rejected raw materials, intermediates or API labeling and packaging materials

Requirement	Description
6.30.1	BioSpectra maintains records that contain the following information: manufacturer, identity, quantity of each shipment, the name of the supplier, supplier's control number, if known, other identification number, if applicable, the number allocated on receipt and the date of receipt in accordance with the Materials Handling Procedure and Label Creation, Approval, and Issuance Procedure.
6.30.2	Analytical Summary Sheets for raw materials, Component Summary Sheets for components, and Finished Good Label Summary Sheets for Labeling, are attached to the respective receiving paperwork.
6.30.3	Use of components and raw materials are traced through production batch records.
6.30.4	Production label review is documented through the Label Accountability Form. Components are inspected in accordance with the Materials Handling procedure.
6.30.5	The final decision regarding raw material, intermediates and API packaging and labeling is documented on the respective summary sheet.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

Requirement	Description
6.31	Master (approved) labels are comprised of the approved label template and the approved label information, which require verification and comparison to issued labels in accordance with the Label Creation, Approval, and Issuance Procedure.

6.4. Master Production Instructions (Master Production and Control Records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the Quality Unit(s).

Requirement	Description
6.40	Master production records are approved in accordance with BioSpectra's MasterControl Document Creation Revision Review and Approval Process procedure for paper-based Batch Records or MasterControl MX Master Template Builder Procedure for Electronic Batch Records in BioSpectra's current electronic document management system. The collaboration team will prepare the master production records and the record will be signed and independently checked by Manufacturing and Quality at minimum.

6.41 Master production instructions should include:

1. The name of the intermediate or API being manufactured and an identifying document reference code, if applicable.
2. A complete list of raw materials and intermediates designated by names or code sufficiently specific to identify any special quality characteristics.
3. An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included.Variations to quantities should be included where they are justified.
4. The production location and major production equipment to be used.
5. Detailed production instructions, including the:
    a. sequences to be followed
    b. ranges of process parameters to be used
    c. sampling instructions and in-process controls with their acceptance criteria, where appropriate
    d. time limits for completion of individual processing steps and/or the total process, where appropriate
    e. expected yield ranges at appropriate phases of processing or time.
6. Where appropriate, special notations and precautions to be followed, or cross references to these
7. The instructions for storage of the intermediate or API to assure its suitability for use, including the labeling and packaging materials and special storage conditions with time limits, where appropriate.

Requirement	Description
6.41.1	Master production records include the names of the Active Pharmaceutical Ingredient or Excipient being manufactured and the DCN (Document Control Number) for paper-based batch records or Master Template identification for electronic batch records, which is the identifying document reference code.
6.41.2	A complete list of raw materials is stated by name in the Master production batch record, which is specific enough to identify special quality characteristics.
6.41.3	Quantities of all raw materials used in the production of Active Pharmaceutical Ingredients or Excipients are clearly defined in the master production records. Additionally, variations are provided where justified and within validation parameters.
6.41.4	Master production records include the location in which the Active Pharmaceutical Ingredient or Excipient is to be manufactured. Additionally, all major equipment used in the manufacturing process is listed and inspected by production personnel prior to manufacturing.
6.41.5.a	Master production records include the sequences of steps to be followed.
6.41.5.b	Master production records include the ranges of process parameters to be used.

Requirement	Description
6.41.5.c	Master production records include sampling instructions and in-process controls with their acceptance criteria, where appropriate.
6.41.5.d	Master production records include time limits for completion of individual processing steps and/or the total process, where appropriate.
6.41.5.e	Master production records include expected yield ranges at appropriate phases of processing or time.
6.41.6	Where appropriate, special notations and precautions to be followed, or cross reference to these are included in the production batch record as instructions and/or procedures in respective reference sections.
6.41.7	Master production records contain specific instructions for packaging and storage of finished good materials.

6.5. Batch Production Records (Batch Production and Control Records)

6.50 Batch Production Records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The Batch Production Record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the Batch Production Record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

Requirement	Description
6.50	Batch production records are prepared for each batch of any material to be produced. Only Quality Unit personnel trained to issue a Batch Record according to the Batch Record Issuance procedure may issue a Batch Record.

6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

Requirement	Description
6.51	Batch Records are numbered with a unique lot number and initialed (signature equivalent) and dated on paper-based batch records or signed and dated on electronic batch records by the issuer according to the Batch Record Issuance procedure.

6.52 Documentation of completion of each significant step in the Batch Production Records (batch production and control records) should include:

1. Dates and, when appropriate, times
2. Identity of major equipment (e.g., reactors, driers, mills, etc.) used
3. Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing
4. Actual results recorded for critical process parameters
5. Any sampling performed
6. Signatures of the persons performing and directly supervising or checking each critical step in the operation
7. In-process and laboratory test results
8. Actual yield at appropriate phases or times
9. Description of packaging and label for intermediate or API
10. Representative label of API or intermediate if made commercially available
11. Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately
12. Results of release testing

Requirement	Description
6.52	Documentation of the completion of each significant step in the batch production records contains the required information listed below.
6.52.1	Dates and times are recorded where necessary within the batch production record.
6.52.2	Identifications of all equipment to be used are explicitly listed within each batch production record.
6.52.3	Specific identification of each batch, including weights, measures, and batch numbers of all raw materials, intermediates and any reprocessed materials used during manufacturing are available in the batch production record.
6.52.4	Actual results recorded for critical process parameters are documented within the batch production record.
6.52.5	Any sampling performed according to the batch production record is noted where appropriate.
6.52.6	The initials (signature equivalent) or signatures of both the performing operator and verifying operator, where applicable, are recorded at the time each critical step is performed.
6.52.7	In-process and laboratory test results are entered and/or attached to the batch production record by Laboratory Services or Production personnel where appropriate.
6.52.8	Actual yield is calculated and verified at the appropriate phases or times.

Requirement	Description
6.52.9	A description of the packaging is contained within the batch production record. A description of the label is included as an attachment to the batch production record.
6.52.10	An approved copy of the label is retained with the batch production record for each batch.
6.52.11	Any deviation is noted on the batch production record and a reference to the full investigation is documented as well.
6.52.12	Results of release testing are documented in Laboratory Notebooks and/or the product specific analytical procedure and in an Analytical Summary Sheet. A copy of the Analytical Summary Sheet at minimum is attached to the batch production record upon completion.

6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

Requirement	Description
6.53	Any critical deviations or failures of a batch to meet specifications are documented through the Discrepancy Investigation procedure. If the determined root cause could conceivably extend as far to effect other batches, all such batches are also investigated.

6.6. Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

1. A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing
2. A statement of or reference to each test method used
3. A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions
4. A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested
5. A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors
6. A statement of the test results and how they compare with established acceptance criteria
7. The signature of the person who performed each test and the date(s) the tests were performed

8. The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

Requirement	Description
6.60	Data derived from all tests conducted in the laboratory are recorded in assigned Laboratory Notebooks or on the product or analysis specific analytical procedure in accordance with the Laboratory Notebooks procedure.
6.60.1	The lot number, material name, and date of analysis are recorded in the Laboratory Notebooks. The date the sample was taken and the quantity, where appropriate, is on the specific label for the respective material. The date the sample was received for testing is available on the Laboratory Sample Log-In Logbooks at each respective Laboratory.
6.60.2	The test method used for each analysis is documented in accordance with the Laboratory Notebooks procedure.
6.60.3	A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions are documented in accordance with the Laboratory Notebooks procedure.
6.60.4	All raw data is available in the Laboratory Notebook or on the specific analytical procedure. All spectra, graphs, and charts, which are not directly in the notebook or analytical procedure are stored in binders and are readily available.
6.60.5	Any calculation utilized during an analysis is recorded within the documented analysis.
6.60.6	A statement of the test results and how they compare with established acceptance criteria is documented on the respective analytical summary sheet.
6.60.7	Documented Laboratory analysis in notebooks and analytical packets require a signature of the analyst performing the test on each page.
6.60.8	Each Laboratory Notebook page and analytical procedure requires a second person signature showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards in accordance with the Laboratory Notebooks procedure.

6.61 Complete records should also be maintained for:

1. Any modifications to an established analytical method
2. Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices
3. All stability testing performed on APIs
4. Out-of-specification (OOS) investigations.

Requirement	Description
6.61	QC laboratory records are maintained adequately for all areas.
6.61.1	Modifications to an established analytical method must be addressed by following the MasterControl Document Creation Revision Review and Approval Process and/or Change Control procedure. Based on this assessment a new analytical method validation may be required.
6.61.2	Periodic calibration of instruments, apparatus, gauges, and recording devices, as applicable, pertaining to the QC Laboratory are dictated by the Calibration and Laboratory Calibration procedures. Individual methods to perform these calibrations may be located in procedures pertaining to each respective instrument.
6.61.3	Stability testing is controlled by the Stability Testing Program.
6.61.4	Any out of specification result will lead to the initiation of an out of specification checklist, which may escalate into a QC Laboratory Investigation. The QC Laboratory Investigation Procedure guides this process.

6.7. Batch Record Review and Approval Procedure

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

Requirement	Description
6.70	The written procedures followed for the review and approval of batch production records and laboratory control records, including packaging and labeling, can be found in the Batch Record Review and Approval procedure, Laboratory Notebooks procedure, Materials Handling Procedure, and Label Creation, Approval, and Issuance procedure.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the Quality Unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the Quality Unit(s).

Requirement	Description
6.71	Batch production and laboratory control records are reviewed by Production and Quality Unit personnel prior to release or distribution of the material in accordance with the Batch Record Review and Approval procedure, Laboratory Notebooks procedure, Materials Handling Procedure.

6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

Requirement	Description
6.72	The Manufacture Batch Record Review Checklist requires that any relevant Discrepancy Investigations, Laboratory Investigations, Supplier Corrective Actions, Pest Sightings, and Complaint logs are completed prior to release of the batch.

6.73 The Quality Unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

Requirement	Description
6.73	Batch production records are reviewed by Production and Quality Unit personnel prior to release or distribution of the material in accordance with the Batch Record Review and Approval and Materials Handling procedures.

7. MATERIALS MANAGEMENT

7.1. General Controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

Requirement	Description
7.10	Material receipt, identification, quarantine, storage, handling, sampling, testing, approval and rejection are described in the Materials Handling procedure and referenced procedures.

7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

Requirement	Description
7.11	All suppliers and service providers are audited in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan.

7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the Quality Unit(s).

Requirement	Description
7.12	Supplier approval testing is designed to confirm that the material is uniform and adheres to all agreed upon specifications.

7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

Requirement	Description
7.13	If the supplier is not the manufacturer of a material, then the name and address of that manufacturer is requested and included in the respective Supplier and Manufacturer List, as appropriate.

7.14 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

Requirement	Description
7.14	Any change in the supply of raw materials is performed according to the Change Control procedure.

7.2. Receipt and Quarantine

7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.

Requirement	Description
7.20	All incoming materials (including containers and groups of containers)are inspected and approved according to the receiving and inspection procedures outlined in the Materials Handling procedure. All materials are held in quarantine status until they have been sampled, examined, or tested, as appropriate, prior to release for use.

7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

Requirement	Description
7.21	All incoming material is stored in Quarantine status in accordance with the Materials Handling procedure. Prior to release of the material, the material must be sampled, analyzed by the Quality Unit, and released for use by the Quality Unit before it is stored with the existing stock in accordance with the Materials Handling procedure.

7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

1. Certificate of cleaning
2. Testing for trace impurities
3. Audit of the supplier

Requirement	Description
7.22	Bulk deliveries made in non-dedicated tankers include assurance of no cross-contamination from the tanker.
7.22.1	Certificate of cleaning is attached to incoming receiving paperwork, where required.
7.22.2	Testing of trace impurities is in accordance with incoming Raw Material Specifications, where required.
7.22.3	Supplier audits are in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan.

7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

Requirement	Description
7.23	Large storage containers, and their attendant manifolds, filling and discharge lines, as applicable, are appropriately identified in accordance with the Equipment Qualification Master Plan and site-specific process equipment identification procedures.

7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition.

Requirement	Description
7.24	All batches of raw materials and components received are identified and appropriate disposition determined using a unique lot number as detailed in the Materials Handling Procedure.

7.3. Sampling and Testing of Incoming Production Materials

7.30 At least one test to verify the identity of each batch of material should be conducted,with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

Requirement	Description
7.30	Incoming raw materials and components are tested to meet pre-determined specifications upon receipt. The material is then either approved or rejected according to the Materials Handling Procedure.

7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Complete analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a complete analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

Requirement	Description
7.31	Supplier Approval testing is performed on at least three incoming batches of any new supplier's material and compared with the Certificates of Analysis in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan.

7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

Requirement	Description
7.32	Hazardous or highly toxic materials, such as gas cylinders are approved based on the manufacturer's Certificate of Analysis. Visual examination of containers, labels, and recording of batch numbers is performed in accordance with the Materials Handling procedure to help in establishing the identity of these materials. The lack of on-site testing for these materials, where applicable, is justified and documented in the Materials Handling procedure.

7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

Requirement	Description
7.33	The sampling plan and methods are determined according to the Sampling Matrix procedure for the Quality Unit, Supply Chain personnel, and Manufacturing personnel.

7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

Requirement	Description
7.34	Locations designated for appropriate sampling are laid out within the Sampling Matrix procedure for the Quality Unit, Supply Chain personnel, and Manufacturing personnel. These locations depend on the nature of the sampling taking place and cleaning to prevent contamination of these areas in accordance with the Material Sampling Room and Packaging Room Cleaning Procedure or Cleaning Worksheet Procedure, as appropriate.

7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

Requirement	Description
7.35	The Sampling Matrix procedure outlines the process for taking samples and appropriately documenting the act of sampling.

7.4. Storage

7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

Requirement	Description
7.40	Adequate handling and storage of materials is ensured by the Product Care, Materials Handling, and Warehousing procedures.

7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

Requirement	Description
7.41	Proper storage of all materials is performed according to the Materials Handling and Warehousing procedures.

7.42 Materials should be stored under conditions and for a period that have no adverse effect on their quality and should normally be controlled so that the oldest stock is used first.

Requirement	Description
7.42	BioSpectra follows a First-In First-Out (FIFO) policy whenever possible, as outlined in the Materials Handling procedure.

7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

Requirement	Description
7.43	BioSpectra does not currently store any materials directly outdoors with the exception of bulk nitrogen. If additional materials require outdoor storage, they will be in suitable containers and the labels will remain legible and containers will be appropriately cleaned before opening and use.

7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

Requirement	Description
7.44	Rejected Materials are identified and controlled according to the quarantine system outlined in the Materials Handling Procedure and Warehousing Procedure.

7.5. Re-evaluation

7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

Requirement	Description
7.50	An adequate re-evaluation date for materials is determined according to the Materials Handling procedure and/or Stability Testing program. Any material held beyond this designated date is to be placed into quarantine until re-evaluation occurs.

8. PRODUCTION AND IN-PROCESS CONTROLS

8.1. Production Operations

8.10 Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

Requirement	Description
8.10	Raw materials for API and Excipient Manufacturing are weighed or measured under appropriate conditions that do not affect their suitability for use. Confirmation of adequate weighing conditions is confirmed through the Manufacturing Scale and Balance Operation and Performance Check procedure.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

1. Material name and/or item code
2. Receiving or control number
3. Weight or measure of material in the new container
4. Re-evaluation or retest date if appropriate

Requirement	Description
8.11	If a material is subdivided for later use in production operations, the container receiving the material identifies material name and/or item code, lot number, weight or measure of material in the new container, and retest date, where appropriate.
8.11.1	Material identification is found on the Sage Tracker ID and/or Production Identification Tag in accordance with the Materials Handling Procedure.
8.11.2	The lot number of the material can be found on the Sage Tracker ID and/or Production Identification Tag in accordance with the Materials Handling Procedure.
8.11.3	Weight or measure of material can be found on the Production Identification Tag affixed to the storage vessel and/or within the ERP system. This is updated any time this value may change.
8.11.4	If a retest date is associated with the material, this can be found in the ERP system through use of the Sage Tracker ID or Production Identification Tag.

8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, Production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

Requirement	Description
8.12	Each critical step within the production batch record contains witness verification by a second operator. Production personnel verify that materials are those specified in the batch record in accordance with the Materials Handling and associated reference procedures.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

Requirement	Description
8.13	Each critical step within the production batch record contains witness verification by a second operator.

8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

Requirement	Description
8.14	Actual batch yields are calculated upon completion of production. Established expected yields are noted within the Batch Record, and any yield found to be outside of the allowable range is investigated according to the Discrepancy Investigation Procedure.

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

Requirement	Description
8.15	Any deviation that might occur is documented and investigated according to the Discrepancy Investigation Procedure.

8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

Requirement	Description
8.16	Production Identification Tags are used to display and regulate the current status of all equipment used in manufacturing.

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

Requirement	Description
8.17	Material to be reprocessed or reworked includes the appropriate controls in accordance with the Materials Handling procedure and Material Reprocessing or Reworking procedure to prevent unauthorized use.

8.2. Time Limits

8.20 If time limits are specified in the master production instruction (see 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

Requirement	Description
8.20	Time limits specified in Master Production Instructions are designed and validated through the Manufacturing Process Validation Master Plan, as well as the Equipment Performance Qualification requirements detailed in the Equipment Qualification Master Plan. Any deviation from a validated time limit is investigated through the Discrepancy Investigation Procedure.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

Requirement	Description
8.21	Intermediates held for further processing are stored under appropriate conditions to ensure their suitability for use.

8.3. In-Process Sampling and Controls

8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

Requirement	Description
8.30	Written procedures are established to control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria are defined based on the information gained during the development stage or historical data.

8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

Requirement	Description
8.31	Appropriate in-process controls are designed according to the Manufacturing Process Validation Master Plan for the respective product. These controls are designed to monitor applicable impurities that may build over time or to confirm specifications crucial to the manufacturing process. These controls may also be used to determine moisture levels or percent purity at the end of manufacturing.

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the Quality Unit(s).

Requirement	Description
8.32	All critical in-process controls, including the control points and methods, are stated in writing within the respective Production Batch Record, Test Method, or associated procedure, and are approved by the Quality Unit at minimum.

8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior Quality Unit(s) approval if the adjustments are made within pre-established limits approved by the Quality Unit(s). All tests and results should be fully documented as part of the batch record.

Requirement	Description
8.33	Any adjustment allowed to be performed by qualified production department personnel is clearly documented within the Batch Record and justification for these pre-established limits is outlined within the validation documentation. All tests and results are fully documented as part of the batch record.

8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

Requirement	Description
8.34	Adequate sampling methods are outlined within the Batch Record and Sampling Matrix procedure. These sampling methods are established during the process validation in accordance with the Manufacturing Process Validation Master Plan.

8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

Requirement	Description
8.35	Adequate sampling methods are outlined within the Batch Record. These sampling methods are established during the process validation in accordance with the Manufacturing Process Validation Master Plan. The Product Care procedure and Materials Handling procedure are designed to prevent contamination and ensure integrity of all materials.

8.36 Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

Requirement	Description
8.36	Out-of-specification investigations are not normally performed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4. Blending Batches of Intermediates or APIs

8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuges loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

Requirement	Description
8.40	Blending operations are performed in accordance with the approved Batch Record for the particular product.

8.41 Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

Requirement	Description
8.41	All individual batches to be blended must be analyzed and approved prior to blending.

8.42 Acceptable blending operations include but are not limited to:

1. Blending of small batches to increase batch size
2. Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

Requirement	Description
8.42	Blending operations adhere to the acceptable conditions listed below.
8.42.1	Blending of small batches to increase batch size is done via a validated or verified process according to the approved Batch Record.
8.42.2	Blending of tailings is not typical to BioSpectra operations.

8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.

Requirement	Description
8.43	Blending processes are adequately controlled and documented in the production Batch Record. The blend is tested according to finished goods testing to ensure quality prior to release.

8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

Requirement	Description
8.44	Blend Batch Records require documentation of all lots to be blended together.

8.45 Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

Requirement	Description
8.45	Blending processes are validated or verified according to the Manufacturing Process Validation Master Plan.

8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

Requirement	Description
8.46	Stability of blended materials is confirmed through stability analysis associated with the validation, where applicable, of the blending process in accordance with the Stability Testing Program.

8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

Requirement	Description
8.47	Expiry or retest dates of blends are assigned according to the manufacturing date of the oldest material in the blend in accordance with Batch Record Issuance.

8.5. Contamination Control

8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

Requirement	Description
8.50	In order to prevent carry over of residual product, batch records and the Cleaning Worksheet Procedure include instructions for cleaning and verification of the effectiveness of cleaning. Additionally, the Process Cleaning Validation Master Plan has been established to develop Cleaning Validation Protocols.

8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

Requirement	Description
8.51	Production personnel are required to adhere to the guidelines set forth by the Product Care and Materials Handling procedures. These procedures include instructions for contamination prevention within the manufacturing process.

8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

Requirement	Description
8.52	Production personnel are required to adhere to the guidelines set forth by the Product Care, Materials Handling, and Gowning Master Plan procedures. These procedures include instructions for contamination prevention within the manufacturing process including how to handle materials after purification.

9. PACKAGING AND IDENTIFICATION LABELING OF APIS AND INTERMEDIATES

9.1. General

9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials.

Requirement	Description
9.10	Written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials are available. These procedures are outlined through the Materials Handling procedure and Label Creation, Approval, and Issuance Procedure.

9.11 Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

Requirement	Description
9.11	Packaging and labeling materials must conform to established specifications prior to release in accordance with the Materials Handling procedure and Label Creation, Approval, and Issuance Procedure.

9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

Requirement	Description
9.12	Component Receiving paperwork, Label receiving paperwork, and the Label Accountability Form are utilized to show the receipt, examination, or testing, and acceptance or rejection of all packaging and labels in accordance with the Materials Handling procedure and Label Creation, Approval, and Issuance Procedure.

9.2. Packaging Materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

Requirement	Description
9.20	All packaging containers must be qualified for use in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan. They must be approved before use upon receipt by BioSpectra according to the Materials Handling procedure Component Inspection process.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

Requirement	Description
9.21	Containers are evaluated and cleaned, as needed in accordance with the Materials Handling procedure and production batch records. Stability studies are used to assure that containers have no effect on the product and therefore are not reactive, additive, or absorptive in accordance with the Stability Testing Program procedure. Packaging for the stability studies is selected in accordance with the Stability Inventory procedure and Quality Assurance issued Stability Checklist. Containers are also approved according to according to the Materials Handling procedure.

9.22 If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

Requirement	Description
9.22	Containers that are re-used are product-dedicated in accordance with the Materials Handling procedure and are cleaned in accordance with the Product Care and Finished Goods Packaging, Sealing and Labeling procedures. All previous labels, if applicable, are removed.

9.3. Label Issuance and Control

9.30 Access to the label storage areas should be limited to authorized personnel.

Requirement	Description
9.30	Access to label materials is restricted to authorized users. Authorized users issue labels according to the Label Creation, Approval, and Issuance Procedure.

9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the Quality Unit(s).

Requirement	Description
9.31	The Label Creation, Approval, and Issuance Procedure details requirements to reconcile the quantities of labels issued, used, and returned. Discrepancies between the number of containers labeled and the number of labels issued are investigated in accordance with the Discrepancy Investigation procedure.

9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

Requirement	Description
9.32	All excess labels bearing batch numbers or other batch-related printing are destroyed if they are not to be used. This destruction is documented on the Label Accountability Form. Returned labels are maintained with the Label Accountability Form and are identified as destroyed by Quality Assurance as indicated and accounted for on the Label Accountability Form.

9.33 Obsolete and outdated labels should be destroyed.

Requirement	Description
9.33	All obsolete labels bearing batch numbers or other batch-related printing are destroyed if they are not to be used. It is not standard practice to retain any obsolete or outdated labels.

9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the Batch Production Record.

Requirement	Description
9.34	Label printers and associated software used to print Finished Good labels for packaging operations are access controlled and at least two labels are printed by Quality Assurance to be retained as part of the Batch Production Record. These labels are verified to ensure conformance to the approved label template and approved label information in accordance with the Label Creation, Approval, and Issuance Procedure.

9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

Requirement	Description
9.35	Once labels are issued according to Label Creation, Approval, and Issuance Procedure, the labels are reviewed by two people and proof of examination is documented on the retained label(s).

9.36 A printed label representative of those used should be included in the Batch Production Record.

Requirement	Description
9.36	A representative label is retained with the batch production record.

9.4. Packaging and Labeling Operations

9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.

Requirement	Description
9.40	The Batch Record, and Finished Goods Packaging, Sealing and Labeling procedure provide personnel with instructions to prepare for Finished Goods shipment and/or storage at all BioSpectra facilities using the correct packaging and labeling materials. The Finished Goods Packaging Inspection procedure details the process that is performed prior to all shipment departures to further ensure that correct packaging materials and labels are used.

9.41 Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

Requirement	Description
9.41	Labeling operations for APIs and Excipients are performed in the area of manufacturing or in the appropriate Packaging Room. This ensures that there is no risk of mix up with other products.

9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.

Requirement	Description
9.42	Labels used on containers of intermediates or APIs indicate the name, the batch number of the product, and storage conditions (where applicable).

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

Requirement	Description
9.43	If the Excipient or API is intended to be transferred outside the control of BioSpectra's material management system, BioSpectra's name and address, quantity of contents, and special transport conditions and any special legal requirements are also included on the label. For Excipients and APIs with an expiry date, the expiry date is indicated on the label and Certificate of Analysis. For Excipients and APIs with a retest date, the retest date is indicated on the label and Certificate of Analysis.

9.44 Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the Batch Production Records, the facility log, or other documentation system.

Requirement	Description
9.44	Packaging and Labeling facilities are inspected before use in accordance with the Pre-Process Room Inspection SOP procedure and per instructions in the Batch Record.

9.45 Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

Requirement	Description
9.45	Packages and labels must be approved by quality and manufacturing personnel prior to use. This dual approval is documented on the Label Accountability Form, as well as on the retained labels. Finished good packaging inspections are conducted prior to shipment to further examine that packaged APIs and Excipients have the correct label.

9.46 Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

Requirement	Description
9.46	Tamper-evident packaging is used for all containers, as appropriate.

10. STORAGE AND DISTRIBUTION

10.1. Warehousing Procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

Requirement	Description
10.10	Warehouse conditions are regularly monitored according to the Temperature and Humidity Monitoring procedure.

10.11 Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been made.

Requirement	Description
10.11	Quarantined, rejected, returned, or recalled materials, if applicable, are stored in accordance with the Materials Handling and Warehousing procedures where the disposition status is maintained in the ERP system to prevent the unintentional or unauthorized use.

10.2. Distribution Procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the Quality Unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the Quality Unit(s) and if appropriate controls and documentation are in place.

Requirement	Description
10.20	APIs and Excipients are only released for distribution to third parties after they have been released by the Quality Unit.

10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.

Requirement	Description
10.21	Prevention of contamination leading up to the time of distribution is controlled by the Product Care procedure. In addition, no departing materials are released prior to completion of a Finished Goods Packaging Inspection. This procedure includes inspection of containers, pallets, trailers, labels, and documentation as detailed in the approved Finished Goods Packaging Inspection sheet.

10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.

Requirement	Description
10.22	A statement of storage conditions and/or transport conditions for API and Excipient material is included on the label, if applicable.

10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

Requirement	Description
10.23	The Bill of Lading, Safety Data Sheet, and Finished Good Label that accompanies each shipment details the storage and transportation requirements. Confirmation that this documentation is accurate and accompanying the shipment is confirmed by the Finished Goods Packaging Inspection.

10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

Requirement	Description
10.24	In the event of a product recall, the Product Recall procedure will be followed. This procedure ensures that proper traceability paths are followed to retrieve all pertinent information. Additionally, this procedure requires the performance of an annual Mock Recall.

11. LABORATORY CONTROLS

11.1. General Controls

11.10 The independent Quality Unit should have at its disposal adequate laboratory facilities.

Requirement	Description
11.10	Each of BioSpectra's manufacturing facilities contains an on-site laboratory. Approved service providers are audited and used for any analysis that cannot be performed at BioSpectra in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan.

11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

Requirement	Description
11.11	Documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data are available. Sampling of materials is performed according to instructions within the Batch Record, and the Sampling Matrix procedure. Testing and approval or rejection of materials is documented within the Laboratory Notebooks or analytical procedure in accordance with the Laboratory Notebooks procedure. Laboratory Records are maintained in accordance with the Record Storage, Retention & Control procedure.

11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the Quality Unit(s).

Requirement	Description
11.12	All specifications, sampling plans, and test procedures are scientifically sound and proven during process and method validations. Specifications, sampling plans, and test procedures are drafted by the appropriate organizational unit and reviewed and approved by the Quality Unit. This is performed in accordance with the Manufacturing Process Validation Master Plan and the Analytical Methods Validation Master Plan. Any changes are documented in accordance with the MasterControl Document Creation Revision Review and Approval Process and/or the Change Control Procedure.

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

Requirement	Description
11.13	Appropriate specifications are established for each API and excipient in accordance with accepted standards or according to customer requirements. These specifications are consistent with the manufacturing process, and impurity-indicating tests are confirmed through the Degradation and Impurity Profiling SOP. Evaluation of all specifications is performed including standard testing, impurity testing and any microbial or endotoxin testing.

11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.

Requirement	Description
11.14	Laboratory procedures are followed and documented at the time of performance in accordance with the Documentation Entry and Error Correction, and Laboratory Notebooks procedure. Any deviations from the above described procedures are documented and adequately explained.

11.15 Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

Requirement	Description
11.15	Any out-of-specification result is investigated appropriately according to the QC Laboratory Investigation procedure beginning with initiation of an Out of Specification Checklist and escalating to a QC Laboratory Investigation, where required. This procedure is divided into two phases and requires analysis of data, impact assessment, corrective actions, preventative actions (where applicable), and material disposition upon completion. If resampling or retesting is performed after the OOS results, then both are performed according to documented procedures.

11.16 Reagents and standard solutions should be prepared and labeled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.

Requirement	Description
11.16	All reagents and standard solutions are stored and/or prepared and labeled according to the Laboratory Chemicals procedure.

11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

Requirement	Description
11.17	Primary reference standards are obtained as appropriate for the manufacture of APIs and excipients. The source of each primary reference standard is documented, and each instance of use is recorded in accordance with the Laboratory Notebooks procedure and Reference Standard Data Card Issuance procedure. Primary reference standards obtained from an officially recognized source are normally used without testing as they are stored under conditions consistent with the supplier's recommendations. BioSpectra may also qualify secondary reference standards in accordance with the Qualification of Secondary Reference Standard procedure. Reference standards are stored in accordance with the Laboratory Chemicals procedure.

11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

Requirement	Description
11.18	Where primary reference standards are not available from an officially recognized source, an "in-house primary standard" is established.

11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

Requirement	Description
11.19	Secondary reference standards are appropriately prepared, identified, tested, approved, and stored in accordance with the Qualification of Secondary Reference Standard procedure and Laboratory Chemicals procedure. Requalification of standards, if required, will occur based on the recommended retest date of the qualified material or on an as-needed basis.

11.2. Testing of Intermediates and APIs

11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

Requirement	Description
11.20	Each batch of material is tested to ensure conformance with that product's specifications. Conformance that is documented in Laboratory Notebooks or on analytical procedures are transcribed onto Analytical Summary Sheets, which reflect specifications based on the product code required.

11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B.

Requirement	Description
11.21	All products are analyzed individually according to the Degradation and Impurity Profiling procedure. This procedure allows for adequate design of impurity profiles of each product so that any plausible impurities may be identified and quantified for further monitoring and control.

11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

Requirement	Description
11.22	An Impurity Profile is executed with each recurring validation of a material. This ensures that any changes in the API or Excipient as a result of any raw material, equipment, or production process changes are detected and documented.

11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

Requirement	Description
11.23	Microbial testing is performed by BioSpectra's approved Service Provider, as required by Batch Records, Validations, Impurity Profiling procedures, and respective Finished Goods Summary Sheets where microbial quality is specified.

11.3. Validation of Analytical Procedures - see Section 12.

11.4. Certificates of Analysis

11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.

Requirement	Description
11.40	A Certificate of Analysis is issued for each batch according to the Certificate of Analysis Issuance procedure.

11.41 Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

Requirement	Description
11.41	A Certificate of Analysis is issued for each batch according to the Certificate of Analysis Issuance procedure. The Certificate of Analysis includes information such as product grade, lot number, manufacturing and packaging dates, and retest dates or expiration dates. Retest or Expiration dates are also included on the label.

11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

Requirement	Description
11.42	The Certificate of Analysis Issuance procedure requires the input of numerical results (if test results are numerical) for all required analyses on each certificate. Certificate of Analysis templates contain the test names and acceptance criteria required for each product code. Reference to compendial requirements are included, where applicable.

11.43 Certificates should be dated and signed by authorized personnel of the Quality Unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address and telephone number of the repacker/reprocessor and a reference to the name of the original manufacturer.

Requirement	Description
11.43	Certificates are signed and dated by the individual preparing the document, as well as a secondary reviewer. Each Certificate of Analysis also contains the name, manufacturing site address and packaging site address.

11.44 If new Certificates are issued by or on behalf of repackers/reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

Requirement	Description
11.44	Certificates are not issued by BioSpectra on behalf of repackers/reprocessors, or agents or brokers.

11.5. Stability Monitoring of APIs

11.50 A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

Requirement	Description
11.50	Stability testing, as required, is guided by the Stability Testing Program procedure. A report is generated at the completion of a stability study to summarize and analyze the results.

11.51 The test procedures used in stability testing should be validated and be stability indicating.

Requirement	Description
11.51	Analytical test methods are validated according to the Analytical Methods Validation Master Plan. A Stability Indicating Protocol is generated for each product in order to determine all analyses that reflect the stability of that specific finished good.

11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API 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.

Requirement	Description
11.52	Stability samples are stored in containers that are the same or simulate the market container in accordance with the Stability Testing Program and Stability Inventory procedures.

11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

Requirement	Description
11.53	As per the Manufacturing Process Validation Master Plan and Stability Testing Program procedure, all validation batches are placed into the Stability Testing Program.

11.54 Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

Requirement	Description
11.54	The Stability Testing Program requires that a minimum of one batch per year of any GMP manufactured material be placed in the Stability Testing Program.

11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months and at three-month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. 9-month testing) can be considered.

Requirement	Description
11.55	BioSpectra does not currently produce any materials with a shelf-life of one year or less. In the event that BioSpectra begins to manufacture such materials, the Stability Testing Program will be updated to reflect an adequate procedure to accommodate this section. Retest dates for all materials including any with a retest date of less than 1 year follow the testing plan in the Stability Testing Program.

11.56 Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.

Requirement	Description
11.56	The Stability Testing Program outlines required temperature and humidity conditions. These conditions are monitored regularly according to the Temperature and Humidity Monitoring procedure.

11.6. Expiry and Retest Dating

11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).

Requirement	Description
11.60	The Stability Testing Program outlines required temperature and humidity conditions. These conditions are monitored regularly according to the Temperature and Humidity Monitoring procedure. Supporting stability information for expiry or retest dating is available in the respective Stability Report.

11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

Requirement	Description
11.61	Upon completion of the Stability Testing Program, a Stability Report is issued for the material. This report reflects conclusions and establishes the basis for creating retest and/or expiry dates for the material. Based upon customer request or agreements, BioSpectra may issue expiry dates but otherwise defaults to issue a Retest Date.

11.62 Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale.

Requirement	Description
11.62	API or excipient expiry or retest dates are assigned based on long-term or accelerated stability studies, as applicable.

11.63 A representative sample should be taken for the purpose of performing a retest.

Requirement	Description
11.63	A representative sample from each selected batch is packaged and subsequently tested according to BioSpectra requirements. Furthermore, one to two extra samples from each batch are added to stability for the purpose of performing a retest, if necessary.

11.7. Reserve/Retention Samples

11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

Requirement	Description
11.70	Finished Good Retain samples of all finished goods produced are retained for a minimum time of 5 years according to the Sample Retention procedure. These samples are separate samples from those that are placed within the Stability Testing Program.

11.71 Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.

Requirement	Description
11.71	Finished Good Retain samples of all finished goods produced are retained for a minimum time of 5 years according to the Sample Retention procedure. These samples are separate samples from those that are placed within the Stability Testing Program. If the expiry date of products is extended beyond this, then the procedure will be evaluated to retain samples for the appropriate amount of time.

11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no Pharmacopeial monograph, two full specification analyses.

Requirement	Description
11.72	Finished Good Retain samples of all finished goods produced are retained for a minimum time of 5 years according to the Sample Retention procedure. Sufficient quantities of Finished Good Material are retained to conduct at least two full compendia analyses or, when there is no Pharmacopeia monograph, a minimum of two full specification analyses.

12. VALIDATION

12.1. Validation Policy

12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

Requirement	Description
12.10	BioSpectra's Validation Master Plans as listed below serve to define policies regarding validation procedures. • Manufacturing Process Validation Master Plan • Analytical Methods Validation Master Plan • Process Cleaning Validation Master Plan • Computer System Validation Master Plan

12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

1. Defining the API in terms of its critical product attributes
2. Identifying process parameters that could affect the critical quality attributes of the API
3. Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

Requirement	Description
12.11	Critical process parameters (CPPs) and critical quality attributes (CQAs) are identified in accordance with the Manufacturing Process Validation Master Plan. This information is used to define reproducible operational ranges.
12.11.1	CQAs are used to define API and Excipient products in terms of critical product attributes.
12.11.2	An FMEA and C&E Matrix is developed in accordance with the Manufacturing Process Validation Master Plan to identify the CPPs that could affect the CQAs.
12.11.3	Validation procedures define set ranges for each CPP being evaluated.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

Requirement	Description
12.12	Methods used to determine quality and purity of the API and Excipient undergo individual method validations (where applicable) according to Analytical Methods Validation Master Plan.

12.2. Validation Documentation

12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the Quality Unit(s) and other designated units.

Requirement	Description
12.20	A validation protocol is established and approved by the designated validation team prior to execution including a member of the Quality Unit. Any changes to a validation protocol that impact the intent of a step during execution must be approved by all parties who approved the protocol.

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.

Requirement	Description
12.21	BioSpectra validation protocols define both CPPs and their acceptance criteria. The protocol also states the type of validation to be executed, whether it is retrospective, prospective, or concurrent, and the required quantity of batches to be manufactured.

12.22 A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

Requirement	Description
12.22	Upon completion of the validation protocol, including approval and analysis, a validation report is issued by the Validation Team or appropriate designee. This report summarizes the results obtained, comments on any deviations observed, and draws the appropriate conclusions on all obtained information.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

Requirement	Description
12.23	Any changes to the Validation Protocol must be documented and approved before the change takes place and may be included in an addendum. This documentation includes justification for any change. Any changes to a validation protocol that impact the intent of a step during execution must be approved by all parties who approved the protocol.

12.3. Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

1. Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
2. Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.
3. Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.
4. Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

Requirement	Description
12.30	Qualification of critical equipment and ancillary systems is completed prior to the start of process validation activities. This includes evaluation of equipment design and IQ/OQ/PQ for each piece of equipment and/or system as per the Equipment Qualification Master Plan.

12.4. Approaches to Process Validation

12.40 Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

Requirement	Description
12.40	Process validation is used to document evidence that the process, when operated within established parameters, can perform effectively and reproducibly to produce an API or excipient meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.

Requirement	Description
12.41	Validation type is determined prior to execution and is selected based on various factors including cost, history, quality and regulatory requirements, and process development in accordance with the respective Master Plan.

12.42 Prospective validation should normally be performed for all API processes as defined in 12.1. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

Requirement	Description
12.42	Prospective validation procedures are normally completed for all API and Excipient processes during initial validation efforts unless otherwise specified in the specific validation protocol.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

Requirement	Description
12.43	Concurrent validation is conducted when data from replicate production runs are unavailable because only a limited number of API or Excipient batches have been produced, API or Excipient batches are produced infrequently, or API or Excipient batches are produced by a validated process that has been modified.

12.44 An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

1. Critical quality attributes and critical process parameters have been identified
2. Appropriate in-process acceptance criteria and controls have been established
3. There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability
4. Impurity profiles have been established for the existing API.

Requirement	Description
12.44	Retrospective validation procedures may be completed for API and Excipient processes after commercial distribution if it is scientifically justified for already established processes based on an approved and scientifically justified approach.
12.44.1	
12.44.2	
12.44.3	
12.44.4	

12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

Requirement	Description
12.45	Retrospective validation procedures include appropriate sampling plans.

12.5. Process Validation Program

12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

Requirement	Description
12.50	The number of process runs for validation is defined based on the product and the nature of the validation. The number of batches for a prospective and concurrent validation will normally be a minimum of three batches, with a typical fourth batch to allow for reprocessing of fines or partials produced from the process. However, more or less validation batches may be required based on the nature of the product and the nature of the manufacturing process.

12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

Requirement	Description
12.51	All critical process parameters are defined in the validation protocol with associated justification and are controlled and monitored during process validation studies.

12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

Requirement	Description
12.52	Impurity profiles are assessed during process validation. The impurity profile is based on the historical data, the degradation and synthesis pathways, and the manufacturing of the crude materials.

12.6. Periodic Review of Validated Systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

Requirement	Description
12.60	Currently all manufacturing processes are evaluated on an annual basis as part of the Annual Product Review. Additionally, the validation of each product is assessed during the Annual Product Review and the need for re-validation is assessed and conducted, as appropriate.

12.7. Cleaning Validation

12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

Requirement	Description
12.70	Cleaning procedures are performed in accordance with the Cleaning Worksheet Procedure. Cleaning validations are conducted at the end of a campaign, prior to product change over. Cleaning validations are conducted in accordance with the Process Cleaning Validation Master Plan.

12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

Requirement	Description
12.71	Actual equipment usage patterns dictate the cleaning required in accordance with the site-specific Cleaning Reference Sheet per the Cleaning Worksheet Procedure. The equipment utilized in the manufacturing of an API or Excipient is also identified in the Cleaning Validation Protocol. In order to measure and document actual carryover and release limits, a quality procedure was developed and implemented to utilize Cleaning Worksheets in accordance with the Cleaning Worksheet Procedure. The Cleaning Worksheets are issued at the time of cleaning and include the requirements for limits, cleaning procedures, analytical methods, training and acceptance criteria for process equipment train release to ensure that each process equipment train is released with acceptable clean limits and product carry-over requirements are met.

12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.

Requirement	Description
12.72	In order to measure and document actual carryover and release limits, a quality procedure was developed and implemented to utilize Cleaning Worksheets in accordance with the Cleaning Worksheet Procedure. The Cleaning Worksheets are issued at the time of cleaning and include the requirements for the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The Cleaning Validation Protocol requirements are detailed in the Process Cleaning Validation Master Plan.

12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

Requirement	Description
12.73	The Cleaning Worksheet states the required sampling methods to be performed for each cleaning activity. The rationale for swab sampling, when applicable, is detailed in the respective Cleaning Reference Sheet.

12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

Requirement	Description
12.74	All analytical methods utilized for detecting residues or contaminants are validated in accordance with the Analytical Methods Validation Master Plan. The detection limit is established during the method validation. Residue limits are practical, achievable and verifiable and based on the worst-case scenario. Limits are calculated in accordance with the Cleaning Worksheet Procedure.

12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

Requirement	Description
12.75	Equipment cleaning/sanitization studies are conducted in accordance with the Process Cleaning Validation Master Plan. Sanitization or disinfection activities intended for bioburden remediation or control are classified as Cleaning Level S. The Environmental Monitoring Procedure: Bangor and Stroudsburg Facility also monitors equipment for processes that require reduced bioburden.

12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

Requirement	Description
12.76	In order to measure and document actual carryover and release limits, a quality procedure was developed and implemented to utilize Cleaning Worksheets in accordance with the Cleaning Worksheet Procedure. The Cleaning Worksheets are issued at the time of cleaning and include the requirements for the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. This allows the monitoring to ensure effective cleaning procedures are used during routine production and also include requirements for visual inspection.

12.8. Validation of Analytical Methods

12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

Requirement	Description
12.80	All analytical methods are validated or verified as appropriate in accordance with the Analytical Methods Validation Master Plan.

12.81 Methods should be validated to include consideration of characteristics included within the ICH guidances on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

Requirement	Description
12.81	Methods are validated in accordance with the Analytical Methods Validation Master Plan to include considerations of characteristics. Furthermore, the degree of analytical validation performed is sufficient to reflect the purpose of the test, which is stated in each analytical validation, as well as the stage of the manufacturing process during the analysis, such as raw material, in-process, and finished goods testing.

12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

Requirement	Description
12.82	All analytical equipment is qualified prior to starting validation of analytical methods.

12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

Requirement	Description
12.83	If analytical methods are required to be changed, then they are processed in accordance with BioSpectra's Change Control procedure, depending on the type of change. Processing through the Change Control procedure ensures the reason for change is stated and appropriate data is obtained to verify the modification produces results that are as accurate and reliable as the established method. All changes to analytical methods further require a Change Request in the Document Management System workflow with changes detailed in accordance with the MasterControl Document Creation Revision Review and Approval Process.

13. CHANGE CONTROL

13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

Requirement	Description
13.10	BioSpectra has established the formal Change Control system as documented in BioSpectra's Change Control procedure.

13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.

Requirement	Description
13.11	The Change Control forms require identification, documentation, review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment, processing steps, labeling and packaging materials, and computer software in accordance with the Change Control procedure.

13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the Quality Unit(s).

Requirement	Description
13.12	Changes are reviewed and approved by the appropriate organizational units including the Quality Unit in accordance with the Change Control procedure.

13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgement should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

Requirement	Description
13.13	Potential impact is evaluated, and changes are classified. Additional testing, validation, and documentation needed to justify the changes are based on scientific judgement and are included within the respective change control in accordance with the Change Control procedure.

13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

Requirement	Description
13.14	The Change Control form requires a list of all documentation that requires creation or revision based on the change. There is a change control implementation follow-up section to document the completion of these requirements to ensure that all documents affected by the changes are revised.

13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

Requirement	Description
13.15	Evaluation of the first batch(es) is completed as required on the Change Control form.

13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

Requirement	Description
13.16	If the process is modified to an extent that would affect stability, this modification would affect validation. All lots produced under validation are required to be placed on the Stability Testing Program.

13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

Requirement	Description
13.17	BioSpectra notifies customers of changes as per the BioSpectra Change Control procedure and current Customer Agreements.

14. REJECTION AND RE-USE OF MATERIALS

14.1. Rejection

14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

Requirement	Description
14.10	The final disposition of all products is clearly defined during the quality Batch Record review. Additionally, material failing to meet specification is rejected and either reprocessed, reworked, downgraded or wasted depending on the cause of the failure to meet specifications.

14.2. Reprocessing

14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

Requirement	Description
14.20	BioSpectra will reprocess material as deemed suitable for reprocessing within validated batch parameters in accordance with the Material Reprocessing or Reworking Procedure.

14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

Requirement	Description
14.21	BioSpectra processes materials in accordance with the Batch Record and Analytical Procedures for in-process controls.

14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-products and over-reacted materials.

Requirement	Description
14.22	BioSpectra does not normally introduce unreacted materials back into a process unless it is part of the established process. If this were required outside of the established process, then it would be performed in accordance with the Temporary Operating Instruction Procedure and/or Discrepancy Investigation Procedure, or the Change Control procedure.

14.3. Reworking

14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.

Requirement	Description
14.30	Rework of a process step will be investigated in accordance with BioSpectra's Discrepancy Investigation Procedure.

14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written, and the batch released once it is found to be acceptable.

Requirement	Description
14.31	Batches that require rework will follow the Material Reprocessing or Reworking Procedure. Rework of a process step will be investigated in accordance with BioSpectra's Discrepancy Investigation Procedure. Instructions or procedures regarding the rework will be approved as a Temporary Operating Instruction and the batch will be subject to appropriate analysis to ensure suitable quality of material. Stability, additional analysis, or validation of material will be determined in accordance with BioSpectra's investigation procedures.

14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

Requirement	Description
14.32	Batches that require rework will follow the Material Reprocessing or Reworking Procedure. Rework of a process step will be investigated in accordance with BioSpectra's Discrepancy Investigation Procedure. Instructions or procedures regarding the rework will be approved as a Temporary Operating Instruction and the batch will be subject to appropriate analysis to ensure suitable quality of material. Stability, additional analysis, or validation of material (including impurity studies) will be determined in accordance with BioSpectra's investigation procedures.

14.4. Recovery of Materials and Solvents

14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

Requirement	Description
14.40	Any recovered materials must meet specifications for their intended use in accordance with the Batch Record or Temporary Operating Instruction, if applicable.

14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.

Requirement	Description
14.41	Any solvents recovered or reused are controlled and monitored in accordance with the Batch Record or Temporary Operating Instruction, if applicable.

14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

Requirement	Description
14.42	Fresh and recovered solvents and reagents that are combined require adequate testing to show their suitability in accordance with the Batch Record or Temporary Operating Instruction, if applicable.

14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

Requirement	Description
14.43	The use of recovered solvents, mother liquors, and other recovered materials is adequately documented in the Batch Record and/or Temporary Operating Instruction, if applicable.

14.5. Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

Requirement	Description
14.50	Returned APIs and Excipients are identified and quarantined.

14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

Requirement	Description
14.51	Returned APIs or Excipients will be reprocessed or destroyed, as appropriate, based on the conditions and quality of the API or Excipient in accordance with the Returned Goods Procedure.

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

1. Name and address of the consignee
2. Intermediate or API, batch number, and quantity returned
3. Reason for return
4. Use or disposal of the returned intermediate or API

Requirement	Description
14.52	Records of returns of APIs or Excipients are maintained in accordance with the Returned Goods Procedure.
14.52.1	Records include the name and address of the customer.
14.52.2	Records include the API or Excipient, batch number, and quantity returned.
14.52.3	Records include the reason for return.
14.52.4	Records include use or rejection of the API or Excipient.

15. COMPLAINTS AND RECALLS

15.10 All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

Requirement	Description
15.10	All quality-related complaints are recorded and investigated in accordance with the Written and Verbal Complaints procedure.

15.11 Complaint records should include:

1. Name and address of complainant
2. Name (and, where appropriate, title) and phone number of person submitting the complaint
3. Complaint nature (including name and batch number of the API)
4. Date complaint is received
5. Action initially taken (including dates and identity of person taking the action)
6. Any follow-up action taken
7. Response provided to the originator of complaint (including date response sent)
8. Final decision on intermediate or API batch or lot.

Requirement	Description
15.11	Complaint records include the following details in accordance with the Written and Verbal Complaints procedure.
15.11.1	Complaint records include name and address of complainant.
15.11.2	Complaint records include name (and, where appropriate, title) and phone number of the person submitting the complaint.
15.11.3	Complaint records include complaint nature (including name and batch number of the API or Excipient).
15.11.4	Complaint records include the date complaint is received.
15.11.5	Complaint records include action initially taken (including dates and identity of person taking the action).
15.11.6	Complaint records include any follow-up action taken.
15.11.7	Complaint records include response provided to the originator of complaint (including date response sent).
15.11.8	Complaint records include final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

Requirement	Description
15.12	Records of complaints are retained. Trends, product-related frequencies and severity are reviewed in order to take additional action where appropriate in accordance with the Leadership Review Procedure and Annual Product Reviews procedure.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

Requirement	Description
15.13	The Quality Unit shall convene a review board whenever an investigation into a discrepancy or complaint indicates the need for a potential recall. BioSpectra follows the Product Recall procedure if required to conduct recalls.

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

Requirement	Description
15.14	The Product Recall procedure designates who should be involved in evaluating information, how the recall should be initiated, who should be informed about the recall, and how the recalled material will be treated.

15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed, and their advice sought.

Requirement	Description
15.15	In the event of a serious or potentially life-threatening situation, local, national and/or international authorities will be informed, and their advice sought.

16. CONTRACT MANUFACTURER (INCLUDING LABORATORIES)

16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this guidance. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

Requirement	Description
16.10	BioSpectra uses only approved outside laboratories for testing purposes, when necessary. These facilities are listed under the approved Service Provider List and are managed in compliance with BioSpectra's Supplier, Manufacturer, and Service Provider Qualification Master Plan. BioSpectra is responsible for the review and final release of all batches tested by these laboratories.

16.11 Companies should evaluate any contractors (including laboratories) to ensure GMP compliance of the specific operations occurring at the contractor sites.

Requirement	Description
16.11	Service providers are evaluated in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan to assess GMP compliance of the specific operations.

16.12 There should be a written and approved contract or formal agreement between a company and its contractors that defines in detail the GMP responsibilities, including the quality measures, of each party.

Requirement	Description
16.12	Written and approved contracts or formal agreements are established in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan or respective quote for a particular service rendered.

16.13 A contract should permit a company to audit its contractor's facilities for compliance with GMP.

Requirement	Description
16.13	Quality agreements and self-audit questionnaires establish permission to audit the respective Service Provider in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan.

16.14 Where subcontracting is allowed, a contractor should not pass to a third party any of the work entrusted to it under the contract without the company's prior evaluation and approval of the arrangements.

Requirement	Description
16.14	All testing conducted by the Laboratory Service provider is documented and documentation is provided to BioSpectra for traceability of product testing. Service Provider testing that requires third party work will require written approval by BioSpectra during the approval of the test performance. A Third-Party evaluation and approval of arrangements would be performed in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan, if applicable.

16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

Requirement	Description
16.15	Laboratory records are held at the service provider site in accordance with the Service Provider's approved document retention policy. This policy is verified in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan.

16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

Requirement	Description
16.16	Change notification is established and confirmed in accordance with the Supplier, Manufacturer, and Service Provider Qualification Master Plan.

17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELLERS

Requirement	Description
17.	BioSpectra may repackage BioSpectra manufactured materials into different packaging configurations for Bio Pharma Grade and above materials. This grade of material follows the quality management system guidelines outlined in this Quality Manual. Bio Ultra Grade materials are outside of the scope of this Quality Manual.

18. APPENDIX A: QUALITY MANAGEMENT SYSTEM LIST

The following list includes references to BioSpectra's Quality Management System. This is not an all-inclusive list, but contains the primary documents used to comply with ICH Q7. Additional procedures including site and product specific procedures may be included within the references section of these procedures and policies or are available within BioSpectra's Document Management System.

DCN	Title
BSI-SOP-0436	Analytical Methods Validation Master Plan
BSI-SOP-0080	Annual Product Reviews
BSI-SOP-0020	Batch Record Issuance
BSI-SOP-0225	Batch Record Review and Approval Procedure
BSI-DGM-0009	BioSpectra Lot Number Identification
BSI-SOP-0150	Building Access Visitor and Security SOP
BSI-SOP-0351	Business Continuity Plan
BSI-SOP-0131	Calibration
BSI-SOP-0032	Certificate of Analysis Issuance
BSI-SOP-0084	Change Control
BSI-SOP-0111	Chemical Hygiene Plan
BSI-SOP-0391	Cleaning Worksheet Procedure
BSI-SOP-0033	Compliance Inspection
BSI-SOP-0079	Compositing
BSI-SOP-0437	Computer System Validation Master Plan
BSI-SOP-0610	Contamination Prevention
BSI-SOP-0377	Data Integrity Procedure
BSI-SOP-0442	Data Recovery Testing Procedure
BSI-SOP-0102	Degradation and Impurity Profiling SOP
BSI-SOP-0137	Discrepancy Investigation Procedure
BSI-SOP-0535	Document Control Library Procedure
BSI-SOP-0010	Documentation Entry and Error Correction
BSI-SOP-0002	Employee Quality GMP Training
BSI-SOP-0392	Employee Required Safety Training
BSI-SOP-0310	Environmental Monitoring Procedure: Bangor and Stroudsburg Facility
BSI-SOP-0164	Equipment Cleaning and Maintenance
BSI-SOP-0049	Equipment Preventative Maintenance
BSI-SOP-0435	Equipment Qualification Master Plan

DCN	Title
BSI-SOP-0220	Facility Housekeeping
BSI-SOP-0103	Finished Goods Packaging Inspection
BSI-SOP-0028	Finished Goods Packaging, Sealing and Labeling
BSI-SOP-0487	Gowning Master Plan
BSI-SOP-0036	Information Technology Security
BSI-SOP-0125	Inspections by Government Regulatory and Environmental Health, Safety, and Security Agencies
BSI-SOP-0297	Intended Use Statements for Certificate of Analysis and Finished Goods Shipping Label
BSI-SOP-0083	Internal Audit
BSI-SOP-0402	Jacobsburg Current Warehousing Plan
BSI-FRM-0004	Label Accountability Form
BSI-SOP-0004	Label Creation, Approval, and Issuance Procedure
BSI-SOP-0580	Laboratory Calibration SOP
BSI-SOP-0135	Laboratory Chemicals
BSI-SOP-0126	Laboratory Notebooks
BSI-SOP-0101	Leaching Study Procedure
BSI-SOP-0046	Leadership Review
BSI-SOP-0219	Majestic Current Warehousing Plan
BSI-FRM-0239	Manufacture Batch Record Review Checklist
BSI-SOP-0292	Manufacturing Process Validation Master Plan
BSI-SOP-0147	Manufacturing Scale and Balance Operation and Performance Check
BSI-SOP-0415	MasterControl Document Creation Revision Review and Approval Process
BSI-SOP-0491	MasterControl MX Master Template Builder Procedure
BSI-SOP-0413	MasterControl Training Module Administration
BSI-SOP-0319	Material Reprocessing or Reworking Procedure
BSI-SOP-0221	Material Sampling Room and Packaging Room Cleaning
BSI-SOP-0056	Materials Handling SOP
BSI-SOP-0552	McConnell Warehousing Plan
BSI-DGM-0011	Organizational Chart
BSI-SOP-0124	Packaging Batch Record SOP
BSI-SOP-0194	Personal Protective Equipment SOP
BSI-SOP-0048	Pest Control
BSI-SOP-0401	Power Outage/Company Shutdown Procedure
BSI-SOP-0006	Pre-Process Room Inspection SOP
BSI-SOP-0252	Preventative Maintenance for Bangor QC Laboratory Instruments
BSI-SOP-0017	Preventative Maintenance for Stroudsburg Laboratory Instruments
BSI-SOP-0293	Process Cleaning Validation Master Plan
BSI-SOP-0034	Product Care
BSI-SOP-0321	Product Code Issuance
BSI-SOP-0065	Product Recall

DCN	Title
BSI-SOP-0009	Production Area Cleaning
BSI-SOP-0067	Production Identification Tags
BSI-SOP-0443	QC Laboratory Data Backup
BSI-SOP-0093	QC Laboratory Investigation Procedure
BSI-SOP-0360	Qualification of Secondary Reference Standard
BSI-SOP-0029	Quality and EHS Policy Statements
BSI-SOP-0393	Quality Control Audit Trail Procedure
BSI-FRM-0419	Quality Control Out of Specification Evaluation Checklist
BSI-SOP-0035	Record Storage Retention & Control
BSI-SOP-0556	Reference Standard Data Card Issuance
BSI-SOP-0019	Result Reporting
BSI-SOP-0064	Returned Goods Procedure
BSI-SOP-0063	Rockdale Current Warehousing Plan
BSI-SOP-0100	Sample Retention
BSI-SOP-0099	Sampling Matrix
BSI-FRM-0835	Service Provider Questionnaire-General
BSI-SOP-0289	Stability Indication Protocol
BSI-SOP-0146	Stability Inventory
BSI-SOP-0136	Stability Testing Program
BSI-FRM-0811	Supplier Corrective Action Request Form (SCAR)
BSI-SOP-0057	Supplier, Manufacturer, and Service Provider Qualification Master Plan
BSI-SOP-0341	Technically Unavoidable Particle Profile (TUPP)
BSI-SOP-0051	Temperature and Humidity Monitoring
BSI-SOP-0003	Temporary Operating Instruction (TOI) SOP
BSI-ATM-0037	USP/EP Purified Water and WFI Testing Methods
BSI-SOP-0047	Warehouse Area Cleaning
BSI-SOP-0062	Warehousing Procedure
BSI-ATM-0005	Water Testing Methods
BSI-SOP-0050	Work Order Procedure
BSI-SOP-0081	Written and Verbal Complaints