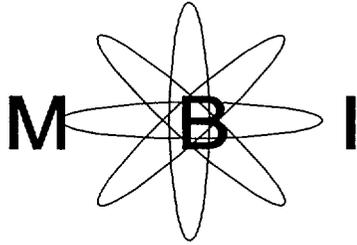


**COPY**



MILLS BIOPHARMACEUTICALS INC.  
120 NE 26th St.  
Oklahoma City, OK 73105  
Phone: (405) 525-3141 Fax: (405) 525-3143

United States Nuclear Regulatory Commission  
Materials Safety Branch  
Division of Industrial and Medical Nuclear Safety  
Two White Flint North  
11545 Rockville Pike Mail Stop 8F5  
Rockville, Maryland 20814

April 30, 2001

Gentlemen:

Enclosed is our amended Sealed Source and Device Evaluation and Registration to include a request for a "series" type product (using Palladium-103) which is equivalent to our original product that uses Isotope Iodine-125. We have highlighted the additional isotope for your convenience showing the changes in relationship to the original isotope (Iodine 125).

We have reduced our Leak Test from 18 hours to 4 hours and made corrections as necessary to support our amendment and updated our Quality Manual which is also enclosed.

There are no associated fees in relationship with this amendment and correction based on our discussions with your office.

If there are any questions please contact me.

Sincerely,

A handwritten signature in black ink, appearing to read 'Stanley Mills', written over a large, sweeping flourish that extends to the left and bottom of the page.

Dr. Stanley Mills Ph.D. R. Ph.

NMSS12  
1/1

# AMENDMENT and CORRECTION TO APPLICATION FOR REGISTRATION OF BRACHYTHERAPY SEED FOR MEDICAL USE

## 10.1 SUMMARY INFORMATION

Mills Biopharmaceuticals Inc.  
120 NE 26<sup>th</sup> Street  
Oklahoma City, Oklahoma 73105  
Telephone Number 405-525-3141  
Facsimile Number 405-525-3143  
e-mail [smills@ionet.net](mailto:smills@ionet.net)

The product is not intended for a Custom User, but for Brachytherapy Seed use.

Mills Biopharmaceuticals is the Manufacturer of these products.

Tradename: ProstaSeed™

Common Name: I-125 Brachytherapy Seed

Models: I-125 SL  
I-125 SH

Common Name: Pd-103 Brachytherapy Seed

Models: Pd-103, SL  
Pd-103 SH

## 10.2 CONDITIONS OF USE

The maximum activity is 5.55 GBq (150 millicuries) + 10% for Iodine Model 125SH and 37 MBq (1.0 mCi) + 10% for Model 125SL. The maximum activity is 185 MBq (5.0 millicuries) + 10% for Palladium Model 103 SH and 78MBq (2.11mCi) + 10% for Model 103SL.

MBI I-125 Brachytherapy Seeds with apparent activities between 3.7 MBq (0.1 mCi) to 37 MBq (1.0 mCi) and MBI Pd 103 with apparent activities between 3.7 MBq (0.1 mCi) to 78 MBq (2.11 mCi) are indicated for permanent interstitial treatment of tumors which are unresectable or residual after excision of the primary lesion, localized, slow growing, and exhibit low to moderate radiosensitivity. Intra abdominal, intrathoracic and superficial tumors may be treated with seeds containing apparent activities within this range. Tumors commonly treated are prostate (early stage), pancreas, head, neck, and lung.

MBI I-125 and Pd-103 Brachytherapy Seeds containing apparent activities greater than 37 MBq (1.0 mCi) and 78 MBq (2.11 mCi) respectively are indicated for temporary interstitial treatment of tumors which are unresectable or residual after excision of the primary lesion, localized, and exhibit moderate radiosensitivity. Temporary implants are indicated in breast, brain and eye tumors.

MBI I-125 and Pd-103 Brachytherapy Seeds are indicated for treatment of residual tumors and recurrent tumors following external radiation therapy, hyperthermia, or chemotherapy or concurrent with these treatment modalities.

### 10.3 CONSTRUCTION OF THE PRODUCT

Each MBI I-125 and Pd-103 Brachytherapy Seed has external dimensions of 4.5 mm  $\pm$  0.3 mm in length and 0.8 mm  $\pm$  0.1 mm in diameter. The cylindrical metal casing is titanium having a wall thickness of 0.05 mm  $\pm$  0.01 mm laser welded at both ends. The laser welding process will be conducted in a steel sealed enclosure. The inert gas nozzles used are constructed and configured to prevent turbulence in the weld area preventing air from entering and contaminating the welds. The inert gas also supplies cooling to the weld after laser termination. The titanium used, A-40 (commercially pure), will be certified by the manufacturer as conforming to the ASTM specification F-67-95 (grade 2), A Standard Specification for Unalloyed Titanium for Surgical Implant Applications. The grade of titanium used and the inert atmosphere of the welds would ensure that there is little or no Oxygen and Nitrogen contamination of the welds. Titanium is a universal material for low energy brachytherapy seed due to its durability, low atomic number, and biocompatibility. (NR-460-S-165-S, NR-460-S-166-S, NR-187-S-103-S, GA-1061-S-101-S, TX-1068-S-101-S, IL-136-S-338-S and GA-645-S-101-S). The silver spheres/carrier for both Iodine-125 and Palladium-103 respectively as silver Iodine or silver palladium are dimensionally 0.5 mm  $\pm$  0.1 mm.

In brief, for the Iodine, the surface of the silver spheres will be coated with silver iodine by incubating activated silver spheres in NaI-125, rinsed with H<sub>2</sub>O, acetone, and air dried. The basic solution of sodium iodine-125 will be used as supplied by the manufacturer.

In brief for the palladium, the surface of the silver spheres will be coated with palladium by a proprietary process, rinsed with H<sub>2</sub>O, acetone, and air dried. The basic solution of ammonium hydroxide palladium-103 chloride will be used as supplied by the manufacturer. The titanium tubing is welded on one end, inverted, the spheres are added, and the remaining end is welded closed. All models have five silver spheres to provide x-ray contrast and support for the radioisotope. An Engineering design drawing is included in the appendix.

### 10.4 LABELING

The size of the individual seeds precludes any engraved, etched, or printed labeling. The seeds are supplied as a group of seeds with an activity within a stated range on the assay date and are packaged in a one-dram vial. Each distribution lot is assigned a unique lot number. A label is affixed to the vial stating: A Caution Radioactive Materials, isotope, activity range, total activity, assay date, and the trefoil radiation symbol, instructions to see package insert and a warning against distribution to unauthorized persons. An additional label is attached to the lead storage container which includes: a Caution - Radioactive Material statement, the trefoil radiation symbol, product description, activity range, total activity, number of seeds, assay date, lot number, instructions to see package insert and a warning against distribution to unauthorized

persons.

## 10.5 PROTOTYPE TESTING

See NRC REGISTRY NR-1081-S-101-S

The palladium 103 is the same as the iodine-125 brachytherapy seed prototypes.

Products of similar design have been used for over 30 years without known operational problems. Nycomed/Amersham (IL-136-S-337-S, IL-136-S-338-S), North American Scientific (CA-0510-S-126-S), Best Medical International (NR-187-S-103-S), Theragenics Corporation (GA-645-S-101-S), and Mills Biopharmaceuticals Inc. (NR-1081-S-101-S,) are currently manufacturing and distributing seeds in the U.S.

Manufacturer	Model	Capsule	Welding	Use	Isotope
Mills Biopharm. Inc.	125SL 125SH	Titanium	Laser	Interstitial Implant	I-125
International Isotope	IS 125	Titanium	Laser	Interstitial Implant	I-125
Amersham	6711/6702	Titanium	Tig	Interstitial	I-125
Best Medical	2300	Titanium	Laser	Interstitial	I-125
International Brachytherapy	1031 L	Titanium	Laser	Interstitial	Pd-103
Theragenics	200	Titanium	Laser	Interstitial	Pd-103
Mills Biopharm Inc	103SL 103SH	Titanium	Laser	Interstitial Implant	Pd-103

## 10.6 RADIATION PROFILES

See NRC Registry: NR-1081-S-101-S

Radiation profiles for Pd-103 will be less than I-125 of similar activity based upon a reduced specific gamma radiation constant from  $7.432 \times 10^{-5}$  mSv/h)/MBq @100 cm for I-125 to  $6.219 \times 10^{-5}$  (mSv/h)/MBq @100 cm for Pd-103 and an estimated palladium 103 attenuation of 55% for 0.05 mm of titanium.

## 10.7 QUALITY CONTROL AND QUALITY ASSURANCE

See NRC Registry : NR-1081-S-101-S

All Quality Control and Quality Assurance will be remain the same with the exception of Leak testing will be reduced in time to 4 hours from 18 hours for both I-125 and Pd-103 sources.

## 10.8 INSTALLATION, SERVICING, AND INSTRUCTIONS TO USERS

See NRC REGISTRY NR-1081-S-101-S

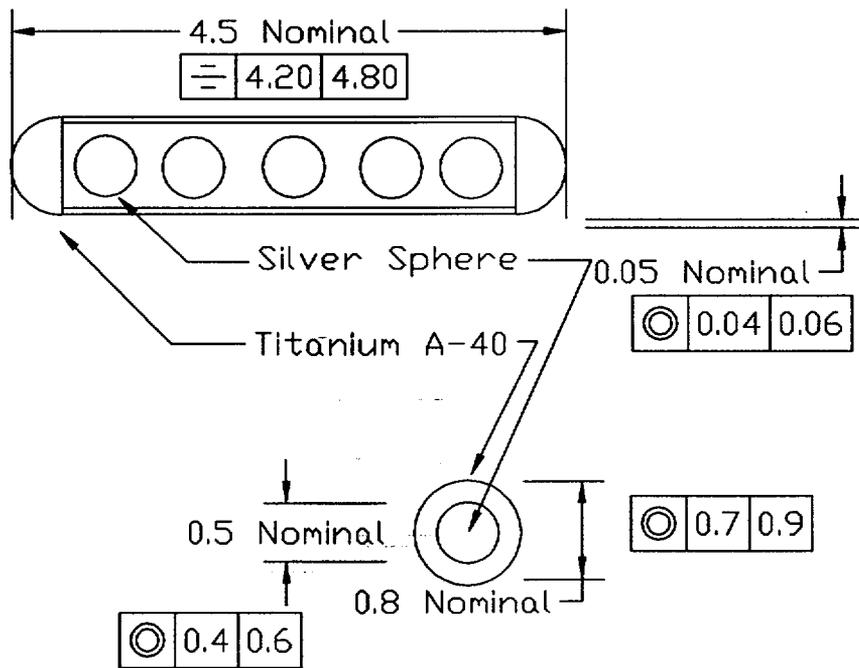
### **I-125 or Pd-103 Brachytherapy Seeds Intended for Permanent Implant**

See NRC REGISTRY NR-1081-S-101-S  
Pd-103 same as I-125.

### **I-125 or Pd-103 Brachytherapy Seeds Intended for Temporary Implant and Reuse**

See NRC REGISTRY NR-1081-S-101-S  
Pd-103 same as I-125.

**APPENDIX A**  
**Drawing of**  
**Mills Biopharmaceutical Sealed Source**  
**follows on next page**





MILLS BIOPHARMACEUTICALS, INC.  
120 N.E. 26<sup>th</sup> Street  
Oklahoma City, Oklahoma 73105  
405-525-3141  
405-525-3143 FAX

# Quality Manual

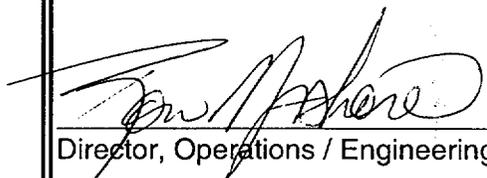
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Document No: QM-1.01

Issue Date: 22OCT99

Revision Date: 30APR01

*PKW  
2/14/01*



Director, Operations / Engineering – Ron Mashore, P.E.

30Apr01  
Date



Director, Quality Assurance – Jacqueline Mills

30 Apr 01  
Date



Chief Regulatory Officer – Terance Grisso

30Apr01  
Date



President / COO – Stanley Mills, Ph.D.

30Apr01  
Date

## Foreword

Mills Biopharmaceuticals, Inc. (MBI) is a Manufacturer of medical devices based in Oklahoma City, OK. MBI was founded in 1992 to produce injectables for clinical trials. In 1995, MBI moved to its present facility and has operated here ever since. In 1997, the injectables product line was dropped and MBI changed its manufacturing practices from cGMP to adopt the Quality System Regulation. MBI re-tooled the production facility from injectables to medical devices. Brachytherapy was started in 1998 with MBI providing production capabilities, which include radioisotope handling, finished product labeling, packaging, and shipping.

MBI is committed to providing consistent processes, safe and efficacious medical devices, as well as meeting our customers requirements.

Our Quality Manual describes the approach maintained by MBI to ensure customer satisfaction through the fulfillment of product requirements and commitments to the company's customers. Adherence to the requirements described in the Quality Manual ensures compliance with the Quality System Regulations—CFR 21 Part 820, Part 11, as well as NRC Regulations.

MBI personnel and resources are dedicated to customer satisfaction. The ultimate measure of our success is the on-time delivery of a safe and efficacious product to our customers.

## Quality Policy

MBI is committed to meet our customer's requirements by providing on-time scheduled delivery of a high quality defect-free product.

## Mission Statement

Discipline, commitment, and perseverance through the full implementation of our Quality System will ensure that our Customers consistently receive the highest level of Product Performance and Product Quality.

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## MANAGEMENT SYSTEM (4.1)

**The MBI management system described in this overview applies to all products produced at MBI and is responsible and committed to the full implementation of a company-wide system of quality and continuous improvement for achieving customer satisfaction and safety. The management system ensures that this is fully understood and maintained at all levels of the organization. The management system is comprised of a series of hierarchically arranged documents, which fully describe the elements of the quality system as well as various business functions (see Appendix II).**

### QUALITY POLICY (4.1.1)

MBI's Quality Policy clearly defines the company's responsibility and commitment to Quality Products and Customer Satisfaction. Dr. Stanley L. Mills is the President and COO. His responsibilities include, but are not limited to: providing the facilities, necessary resources, and qualified personnel to consistently maintain an effective Quality System to produce defect-free products and maintain MBI's Quality Policy. He shall appoint, and document such appointment of, a member of management who, irrespective of other responsibilities, shall have established authority over the Quality System implementation.

Management's commitment to the responsible implementation of MBI's written procedures and controls ensures that products meet quality standards established by customers requirements, internal company specifications, and regulatory agencies. Additionally, it is Management's responsibility to identify, plan, implement and evaluate on-going process improvements, set specific goals, provide related guidance, and support open communications at all levels of the organization to achieve customer requirements.

Management conducts regularly scheduled reviews to assess progress and effectiveness of the Quality System. These reviews include, but are not limited to reviewing internal audit results, customer complaints, production performance, nonconformance and personnel job functions. These reviews are conducted as a mean of achieving and maintaining MBI's Quality Policy.

## ORGANIZATION (4.1.2)

All employees at MBI are responsible for ensuring the manufacturing of a quality product and support the company's commitment to customer satisfaction. Ultimately, it is the responsibility of the total management to verify compliance with the Quality System and provide guidance in the identification, verification and implementation of solutions to correct/prevent nonconformance and the improvement of process control. The Organizational structure of MBI is identified in Appendix I.

Documentation is in place to establish the appropriate responsibilities, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality, and to provide the independence and authority necessary to perform these tasks. Procedures are in place to identify training needs and to ensure that all personnel are trained to adequately perform their job. Training shall be documented.

## QUALITY ASSURANCE PROGRAM (4.2)

A quality assurance program has been established to cover all the operations of Mills Biopharmaceuticals, Inc. This program is in effect throughout the entire company and is documented by written procedures.

All products are issued run/batch/lot numbers and are manufactured in accordance with the Quality System Regulation (21 CFR Part 820), using formal manufacturing documents. The control of these documents are in accordance with established written procedures.

All raw materials and final products are released based upon a series of tests and specifications. Until release, products are segregated by specific identity numbers and await disposition (i.e., Quarantine, Release, Reject) until testing and review is completed. All testing and specifications are established in a series of documents, in which any changes must undergo a revision and review/approval process. Quality does final release of all products.

Non-conforming materials are documented and reviewed as required by the Material Review Board (MRB) procedure. The MRB is made up of members from all departments involved in the process. The board will assign corrective action and/or preventive actions to eliminate the recurrence of the failure or non-conformance.

Departmental procedures are formalized and available to the areas and individuals having designated responsibilities. The procedures cover all functions of the given department.

Customer inquiries and complaints are investigated by Quality Control / Quality Assurance. Products that have been distributed and do not meet specification are subject to a recall procedure, if applicable.

All activities affecting product quality are carried out under conditions that are suitably controlled to ensure that the right equipment and materials are used in the correct area and manner. Personnel in these areas are properly trained in the use of equipment as well as in the importance of Quality to the organization.

The status and adequacy of the Quality Assurance Program is reviewed periodically to insure that the quality of all products produced by this facility is maintained and continues to meet regulatory requirements. This is accomplished by review of each Standard Operating Procedure, with revisions as necessary, and internal audits.

This Quality Manual is a formal and factual representation of the Quality Assurance Program and is reviewed by executive management every two years from issue date, with revisions and updates as necessary, to reflect the current program status.

## Contract Review (4.3)

Documented procedures shall be established and maintained for contract review and for the coordination of these activities. Each tender, contract and/or order will be reviewed to ensure that:

- a) the customer's requirements are adequately defined;
- b) any differences between the contract or accepted order requirements and those in the tender are resolved; and
- c) the company has the capability to meet the contract or accepted order.

How an amendment to a tender, contract or order is made and correctly transferred to the functions concerned within the organization will be identified and documented. Records of contract review will be maintained.

Following documented procedures, contracts are reviewed prior to being accepted. Contracts are reviewed to ensure: customer requirements are understood, differences between the customer's requirements and MBI's performance claims/policies/capabilities are discussed and resolved, all regulatory requirements are adhered to, and, ultimately, MBI can provide goods and services which meet or exceed the customer's specified requirements.

## EQUIPMENT (4.4)

Documented procedures to control, calibrate, maintain inspection, measure and test equipment used to demonstrate the conformance of product to the specified requirements shall be established and maintained. All such equipment that requires calibration is calibrated in a manner traceable to NIST standards, Accredited Dosimetry Calibration Laboratory, U.S. Pharmacopeia, British Pharmacopeia, European Pharmacopeia, Japanese Pharmacopeia, or equivalent where necessary.

Where test software or comparative references are used as suitable forms of inspection, validation or qualification, as appropriate, will prove that they are capable of verifying the acceptability of the product. Records shall be maintained for document control.

Calibration activities are conducted in accordance with documented procedures, to ensure that all equipment requiring calibration is identified and calibrated on schedule. Calibration data and associate corrective action are recorded and maintained by Quality Assurance. Calibration labels, including last and next calibration dates, are attached to calibrated equipment, if possible. Any equipment not requiring calibration is labeled as such.

Calibrations may be performed by an approved calibration vendor, trained MBI employees, the equipment manufacturer/authorized dealer, or other qualified (third-party) personnel.

Some equipment used in the manufacturing of the device may be checked for accuracy and/or acceptable operation on a periodic basis. Equipment history logs will be maintained for each piece of equipment, which requires calibration, use, and maintenance as described in the written procedures.

## DESIGN CONTROL (4.5)

In order to ensure that the specified requirements are met, documented procedures to control and verify the design of the product shall be established and maintained.

Design input requirements relating to the product, including applicable regulatory requirements, shall be identified, documented and their selection reviewed for adequacy. Design output shall be documented and expressed in terms that can be verified and validated against design input requirements.

At defined stages of the design process, formal documented reviews of the design results shall be planned and conducted. Participants at each design review shall include representatives of all functions concerned with the design stage being reviewed. Records of such reviews shall be maintained.

MBI establishes, implements and maintains documented design control procedures to ensure that specified design requirements are met. These procedures address design and development planning, organizational and technical interfaces, establishing design input requirements, evaluating design outputs, reviews, verification, validation, and design changes. A design history file is maintained to ensure the device is developed in accordance with the approved design plan.

## **DOCUMENT CONTROL AND DATA CONTROL (4.6)**

Documented procedures that control all documents and data relating to the requirements of the Quality System Regulation shall be established and maintained.

All documentation required to ensure MBI's products and processes meet internal and regulatory requirements is controlled and available at the point of use either in hard copy or electronically. All controlled documents are clearly identified by a unique control number. Status of all controlled documentation is available either electronically or in hard copy to assure that only the most current versions of documents are in use. Not all copies of a document are required to be controlled. Uncontrolled copies are for reference use only and may not be used in the final acceptance of products. It is the responsibility of the user and the documentation coordinator to ensure they have the latest copy of any controlled document.

A documentation approval and distribution process exists at MBI to ensure that all responsible and affected departments review and approve internal documents prior to release and that they are made available for use in a timely manner.

The distribution, purging and obsolescing of all controlled documentation is accomplished as necessary through on-going database and hard copy management. Approval, storage, distribution, updating, purging, and obsolescing of all controlled documents are the responsibility of Quality Assurance and the functional department's management for which they are generated. Documents of external origin are also controlled within the Document Control system.

## **MATERIAL and SERVICE PROCUREMENT (4.7)**

MBI establishes, implements, and maintains documented procedures to ensure that purchased products conform to specific requirements. Documents contain or reference the material and component identification requirements, drawings, specifications, test and inspection requirements, and special instructions, as needed.

Changes and revisions to procurement documents are subject to the same review and approval procedure as the original document. Procedures are established for the requirements for reporting and approving disposition of nonconformance.

Suppliers are selected on the basis of their ability to meet specified requirements for product, delivery and technical support. Quality Assurance and/or qualified personnel maintain an effective system for selecting qualified suppliers and for monitoring supplier performance to ensure on-going capability.

## **INVENTORY (4.8)**

MBI establishes, implements and maintains documented procedures to ensure proper handling of all inventory, purchased raw materials, in-process materials, and/or finished devices.

Identification, special handling, labeling, and segregating are all part of the process inventory prior to being released for use. Documentation for the handling of all inventory is maintained on hard copy as well as electronically. Any non-conforming materials which are identified, either in-process or finished device, is immediately labeled rejected and segregated to prevent usage of the wrong material. There are written procedures which describe the handling of non-conforming materials.

When applicable, traceability to a supplier's lot number or material identification number is established at the time of product receipt or during receiving inspection, and maintained throughout the subsequent product processing. Also, when applicable, the inventory is labeled with an expiration date to provide for First In, First Out (FIFO), when possible.

Finished products are identified and controlled through the use of a unique batch/lot numbering system to ensure traceability as well as the release for distribution.

## **PROCESS CONTROL (4.9)**

MBI has identified production processes and maintains documented procedures to ensure that these processes are carried out under controlled conditions (i.e., suitable environment, appropriate equipment, etc.). Prior to initiating and/or approving new processes, equipment and material, MBI performs qualifications to ensure their efficiency. Qualifications are controlled documents, and the data is recorded and kept on file.

Procedures are provided and readily available in all manufacturing processes. Trained employees shall manufacture products and monitor process and product quality in compliance with current documented procedures and applicable standards and/or regulations. Flowcharts have been established to describe the flow of material as well as the process, which include quality verification points.

## **PRODUCT IDENTIFICATION and TRACEABILITY (4.9.1)**

All finished devices are labeled through a controlled process and given a batch number which provides traceability. MBI maintains written procedures which describe the product run/batch/lot numbering system.

## **INSPECTION, TESTING and LABELING (4.9.2)**

To prevent nonconformance and ensure product integrity, MBI has documented procedures for the inspection and testing of incoming materials, in-process materials, and finished products.

In-process testing is performed per written procedures by either Manufacturing or Quality Control. Nonconforming materials are identified and segregated until a disposition is established. This ensures that only products that conform to specification are used for further processing.

Final inspection and testing is conducted by the Quality Control department in accordance with written procedures. Final inspection and testing requires evidence that the product has been tested and approved, providing evidence that the product meets all specified requirements. Any product that does not conform is identified and secured in a designated quarantine location until a final disposition is determined. As per written procedures, all inspections are performed by someone other than the person who performed the work. All written records are reviewed and approved prior to release.

No product is shipped until a) all the documented procedures in the device master record have been completed, and b) all the documentation has been reviewed and authorized for release by the appropriate personnel (i.e., Quality Control and/or Quality Assurance).

## **CONTROL OF NON-CONFORMING MATERIALS (4.10)**

MBI has written procedures for the identification, documentation, segregation, evaluation, disposition, and destruction of a nonconforming product.

Non-conforming products are identified and placed into a designated rejected location until a final disposition is determined. A Non-conforming Material Report (NCRM) is prepared and tracks the status of the product.

A disposition to 'return to supplier' or 'destroy' will be prepared and approved by the appropriate personnel. Non-conforming material that is re-processed, according to written procedures, is subject to the same level of inspection and testing as the original process.

Records of all non-conforming materials/finished devices are kept for trend analysis and for verification that the materials or device were not used or released for use.

### **CORRECTIVE and PREVENTATIVE ACTION (4.10.1)**

Corrective action is defined as those actions initiated to permanently correct problems and non-conformance related to specific processes and products. Preventative action is defined as those actions initiated that prevent the occurrence or reoccurrence of problems and non-conformance across a wide range of products or processes.

The corrective and preventative action effort identifies the root cause of a problem or non-conformance, develops an effective solution, and verifies that the problem or non-conformance has been resolved. The effort may include changes to existing procedures as well as the application of process controls to ensure prevention.

The Quality Assurance department or designee is responsible for ensuring the effectiveness of the corrective and preventative action effort and for evaluating unresolved issues to appropriate levels of management.

## **PACKAGING and TRANSPORTATION (4.11)**

Throughout the Quality System, MBI has written procedures for the handling, storage, packaging, and delivery of finished products to prevent damage, deterioration, or unsafe handling.

To prevent damage and/or deterioration, all products that require it are stored in temperature-monitored storage areas. Reagents, chemicals, in-process materials, or other consumables that have a shelf life are assigned expiration dates. Critical items are supported by real-time studies or stability data provided by manufacturers.

Packaging and shipping containers are designed and constructed to assure that the product is adequately protected during storage and distribution, and to conform with any applicable regulatory requirement of both the shipping and receiving destinations. Qualification studies of the shipping container and packaging material are performed prior to the approval of the container.

Only products that have been released for shipment are available in the appropriate storage areas. Written procedures are detailed to ensure compliance with regulations.

Carriers of hazardous materials are selected to ensure that final products arrive at the intended destination in the best condition possible.

## **DEVIATIONS and CUSTOMER COMPLAINTS (4.12)**

Written procedures describing the handling of all written and oral complaints, inquiries, or requests for information regarding a product manufactured and distributed by the facility, have been established.

These procedures include provisions for review and evaluation by Quality Control/Quality Assurance, and an investigation by the appropriate department/personnel.

A written record of each complaint shall be maintained in a file and will include, but not limited to, the product name, catalog number, lot number, customer location, and name of the individual/facility using the product. The appropriate response to the complaint will be prepared according to written procedures and all applicable regulations.

## **CONTROL OF INTERNAL AUDITS (4.13)**

MBI's Quality System includes internal monitoring to ensure the system is effectively implemented and maintained. Audits are performed in accordance with pre-established written procedures or check lists and conducted by personnel not having direct responsibilities in the areas being audited. Each element of the QA Manual is audited at least every two years.

Quality System audits are scheduled on the basis of the status and the importance of the activity performed. Audit observations are documented and corrective actions reviewed for compliance and adequacy. Audit observations are reviewed with management having responsibility in the area audited. Deficient areas shall be re-audited on a timely basis to verify implementation of corrective actions.

## **QUALITY RECORDS and DOCUMENTATION (4.14)**

MBI's quality system requires maintaining readily accessible and legible historical files of documents pertaining to quality. The retained information includes, but is not limited to, records of customer requirements, contract reviews, management reviews, operating logs, audit reports, inspections, tests, material analysis, qualification of personnel, standard operating procedures, and equipment qualification. Other documentation including drawings, specifications, purchasing documents, calibration procedures and reports, non-conformance reports, deviation reports, and corrective action reports. Internal quality records are retained for a period of not less than (3) years. Quality records required to satisfy various regulatory mandates or customer requirements are retained in accordance with the applicable regulation or contract specification.

All records pertaining to each product lot are maintained in a designated controlled area. Records are available for review by authorized personnel only and are filed in numerical order by Product and Lot Number. Records pertaining to production lots shall identify the person performing the test, inspection, or manufacturing step, as well as identifying the product by name, product number, and/or lot number.

### **CONTROL OF QUALITY RECORDS (4.14.1)**

Written procedures are in place to control all records, data and procedures generated at MBI.

### **TRAINING (4.14.2)**

Employee training, combined with documented procedures and instructions, provide the foundation for assuring consistency and conformity in all tasks which impact the quality of our products.

All training performed is based on an in-depth process of needs assessment which evaluates the training, education and experience required for positions which may potentially impact the quality of MBI products. As new or repetitive training requirements are identified, they are applied to their respective areas.

It is the responsibility of all functional supervisors to assure that employees are qualified and training needs are fulfilled. Training records are maintained for all employees. Training criteria and materials are maintained for all training performed and evaluated for content prior to use by the instructor/supervisor.

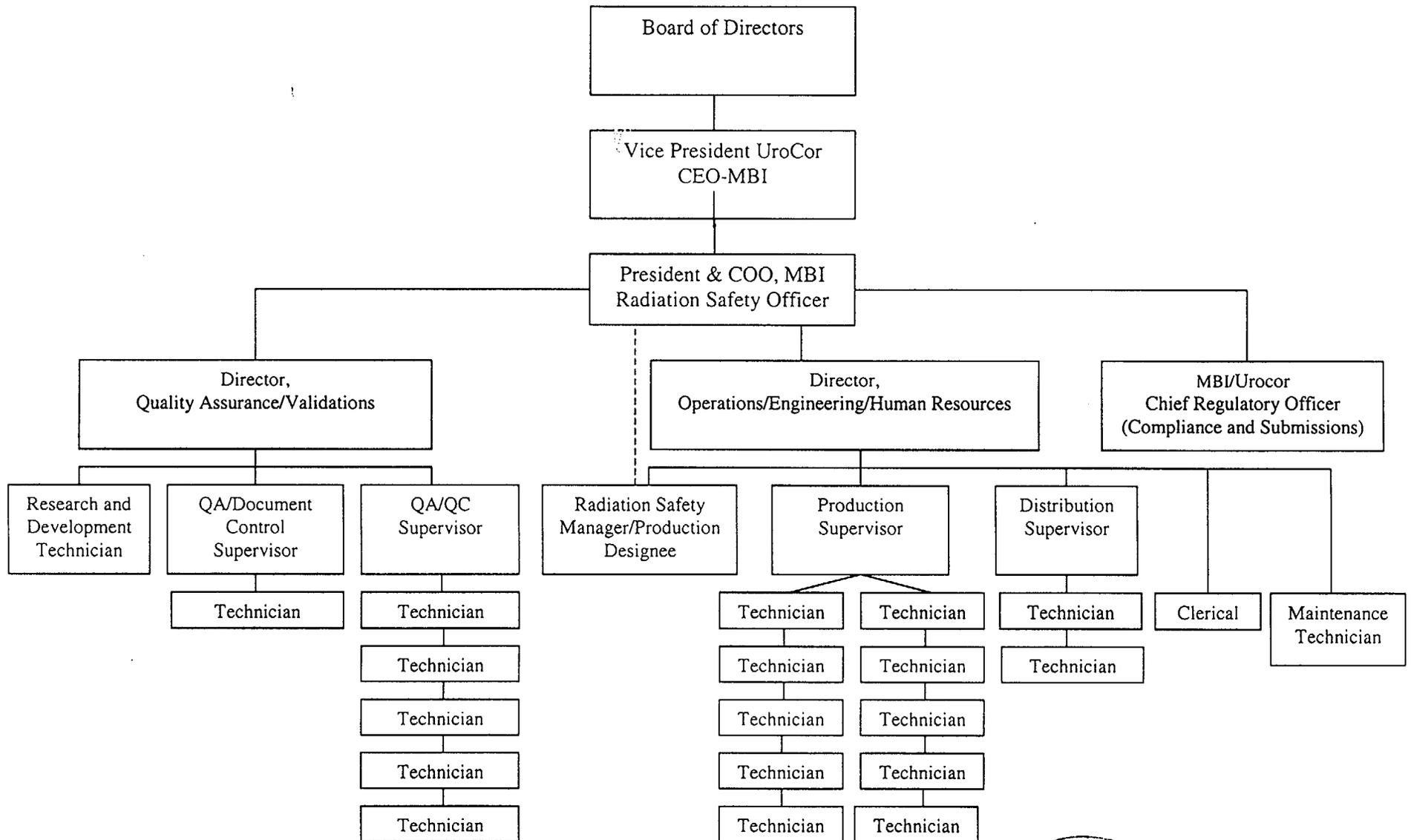
## STATISTICAL TECHNIQUES (4.15)

Statistical techniques are strategically selected and applied at MBI so non-conformance can be prevented. Emphasis is placed on controlling the variability, which causes non-conformance, and on preventing defects to subsequent stages of the process.

The quality system includes the use of appropriate statistical techniques. These techniques include methods for monitoring and improving processes through the evaluation and analysis of statistical data. Results of statistical data analyses provide guidance in the continuous improvement of our processes as well as corrective and preventative action. Statistical methods used at MBI are derived from established standards.

## Appendix I: Organizational Chart

# Mills BioPharmaceuticals (MBI) Organizational Chart



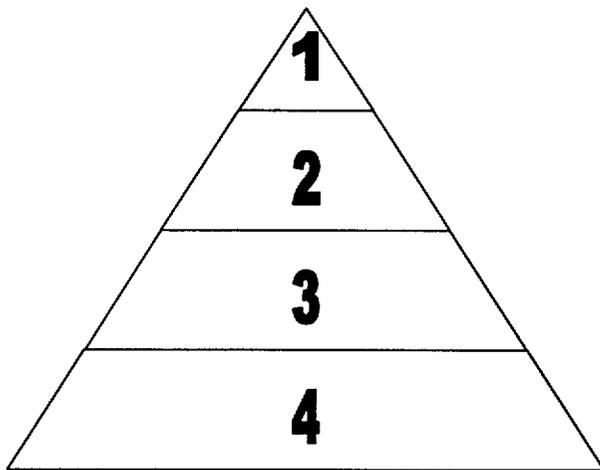
Approved:

Date:

*[Signature]* 05 Mar 01  
Stanley Mills-- President, MBI

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## Appendix II: Quality System Documentation



**Level 1 - Quality Policy and Quality Manual**

**Level 2 - Quality System Processes**

**Level 3 - Procedures and Work Instructions**

**Level 4 - Records and Forms**

## Appendix III: Product Process Flow Chart

