1.) Scope:
Pharmco Products, Inc. is committed to adhere to the applicable requirements of cGMP, as detailed in our Quality Manual. In accordance with this commitment, Pharmco is in the process of validating all the required components. Validation is responsibility of the Quality Control Department.

This SOP describes policy and procedures and Master Plan for validation of chemical producers, products, processes, test methods, equipment, and cleaning techniques.

2.) Normative References:
The following is a list of standards and guidelines deemed to be appropriate for this project. cGMP requirements are used only when applicable as detailed in Pharmco Quality Manual and this document. This list is not exhaustive and further regulations and guidelines will be used where appropriate. The list will be reviewed and revised as necessary whenever a new revision of the SOP is issued.

1. ANSI/ISO/ASQ Q9001:2000  Quality management systems - Requirements
3. ACS Reagent Chemicals (current edition)
4. 21 CFR Current Good Manufacturing Practices (cGMP); Final Rule
6. SOP 4-2-2- Quality Manual
7. SOP 4-2-3-C Document and Data Control
8. SOP 7-5-1-G cGMP Procedures
9. SOP 6-3-0-B Preventive Maintenance of Production and QC Equipment
10. WI IQ-OQ-PQ Program for Critical Equipment
11. SOP 6-2-2-J Training Effectiveness and Verification
12. SOP 7-5-1-I Change Process Control
13. Form QA357 Validation Status Spreadsheet
14. Form QA340 Pharmco Change Control Notification
3.) **Terms and Definitions:**

**Validation:** Establishing, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled. In this respect, **to validate** is to show that a particular process or system performs as required; to demonstrate that a producer supplies product acceptable to our requirements; to demonstrate that a piece of equipment is operating at the expected level of performance.

**Verification:** Confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

**Qualification:** Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Process by which a product is checked to make sure its meets the quality standards set forth in published monograph for the intended grade.

**Prospective Validation:** Establishing documented evidence that a process, procedure, system, equipment or mechanism used in manufacture does what it purports to do based on a pre-planed validation protocol.

**Retrospective Validation:** Validation of a process or a product, which has been marketed based upon accumulated manufacturing, testing and control data.

**Installation Qualifications (IQ):** Establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer’s approved specification and that the recommendations of the supplier of the equipment are suitably considered.

**Operational Qualifications (OQ):** Verification that components of equipment being qualified operate as intended and that the operation is reliable and reproducible within established limits and tolerance. Establishing by objective evidence process control limits and action levels, which result in product that meets all predetermined requirements.

**Performance Qualifications (PQ):** Establishing by objective evidence that the equipment being qualified operates as it is intended and that the performance is reliable and reproducible within the desired limits and tolerances, as identified by Pharmco in our IQ-OQ-PQ program; that the process under anticipated conditions, constantly produces a product which meets the quality standards set forth in published monographs for the intended grade.

**Validation Master Plan:** Document that describes the overall company commitment to validation and further defines key elements of a qualification and validation program.
Validation Report: Controlled document that describes how to perform a specific validation event, and in which the records, results and evaluation of a completed validation program are assembled.

4.) Application:
- All chemical producers supplying raw material to Pharmco
- All raw materials supplied by the producers
- All Critical Equipment as identified on the “Critical Equipment List”
- All special processes / procedures including cleaning procedures
- All non-monograph or substituted analytical test methods

5.) Text:
Validation Philosophy
We recognize that the Life Science Industry is requesting more validation work to be performed by raw material suppliers such as Pharmco. However we also recognize that while these studies are required of the Pharmaceutical Companies themselves, they are not required for raw material suppliers nor are they required to manufacture and certify products according to USP/BP/EP or other compendia.
In addition, Pharmco, like so many other raw material suppliers simply does not have the resources to conduct validation studies to the level performed by Pharmaceutical companies. Therefore, Pharmco has initiated an on-going project to “validate” our suppliers, raw material, critical equipment, cleaning methods, test methods and other processes. In this regard both historic data (retrospective validation) and newly generated data (prospective validation) is used to compile validation data and complete validation reports.
This SOP and the VMP are intended to be ‘live’ documents that support the operation, maintenance and change of the facility for its entire life. VMP provides the basis for validation and quality system activities required for applicable cGMP compliance. This enables the validated production, processing, storage and distribution of products under the control of an appropriate quality system.
The VMP may be revised as appropriate to incorporate changes and/or additions to the facility and/or products.
The validation steps and activities are designed to address all critical product attributes and process steps while minimizing un-necessary work. This is achieved by focusing validation activity onto those systems critical to product quality.
The validation process follows these basic categories:
- Producers Validation
- Products Validation
Pharmco hopes to capture every element of each category above. This is an ongoing process as the company continues to grow and change.

**Producers** have to be validated: In this sense material for that producer has to be qualified as meeting the specifications of the intended grade. In addition the producer is asked to fill out a quality survey establishing their production and quality process.

**Products** have to be validated. Three different lots of the product have to be qualified. If the producer is well established for a particular product and the Certificates they supply pass and at least one lot of the material has passed then the material can be used as validation is being completed on additional lots as long as the material passes all tests for each lot received according to our normal procedures.

**Processes / Procedures:** Validation applies to special processes. According to cGMP, a special process is one in which the quality or effectiveness of the process cannot be adequately tested or evaluated in the final product. All other processes will be verified. Any process that contributes to the final quality of the product that does not get redundantly tested for lot to lot has been validated. For instance, 0.22 micron filtration always removes residue far in excess of the 10 PPM standard. This process has been validated.

*Example #2:* Validation study for Gamma Irradiation. The process of sterilization of SDA-3A, 70% by gamma irradiation was validated to show effectiveness.

**Cleaning Procedures:** Whenever practical, Pharmco adheres to using dedicated equipment in the manufacturing processes. However, in some cases, the same equipment may be used for processing different products. To avoid contamination of the following product, adequate cleaning procedures are essential. Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment, which is suitable for processing of the product. Objective of the cleaning validation is the confirmation of a reliable cleaning procedure so that the analytical monitoring may be omitted or reduced to a minimum. The flushing of the lines has been validated. We have validation work to show that flushing the lines to produce a residue of any previous solvent not in excess of 10 PPM will allow for the new solvent to pass any intended grade. Therefore, this is a
validated cleaning process. The line still has to be verified to be clean but the cleaning process has been validated.

**Equipment**: Reliability of manufacturing, measuring and testing equipment operation and performance must be assured. This assurance supports the validation of products, produced and analyzed using abovementioned equipment. All equipment listed on the “Critical Equipment List” is validated. Equipment validation has been performed as a three-phase process consisting of Installation Qualifications (IQ), Operation Qualifications (PQ) and Performance Verification (PQ). All of our analytical instrumentation has been validated. This is part of our IQ-OQ-PQ program. For example, the 831KF Coulometer was installed in January 2005. IQ-OQ was performed by qualified technician from the supplier, PQ was performed by Pharmco QC personnel. The validation acceptance criteria were established and performance verification procedures were set up in accordance with these criteria.

**Analytical Test Methods**: According to cGMP regulations [21 CFR 211.194(a)(2)], users of analytical methods described in the USP/NF are not required to validate accuracy and reliability of these methods. However, if one analytical method is replaced by another suitable analytical method, a validation study will be established. For example, in order to use existing equipment for performing required USP testing for organic volatile impurities an alternative GC method was created and validated by Pharmco QC personnel.

### VALIDATION MASTER PLAN (VMP)

#### 1.0 VALIDATION STEERING COMMITTEE

1.1 Membership of Validation Steering Committee

This Validation Master Plan has been compiled by Quality Control Department personnel under the direction of the Vice President of Quality Management and approved by a Validation Steering Committee (VSC) who is also managing its execution. The members of the VSC are listed below.
1.2 Responsibilities

With respect to the activities outlined in this VMP, including cleaning, manufacturing practices and analytical methods, the responsibilities of key VSC members are outlined below. Their responsibilities with respect to the overall operation are included where this may have an impact upon validation activities.

Approval of new or amended documentation should be accomplished with the minimum of delay to facilitate the efficient operation of the facility.

1.2.1 Vice President of Quality Management

The Vice President of Quality Management is responsible for:

- Ensuring that appropriately qualified personnel are appointed.
- Ensuring production processes are in accordance with applicable cGMP requirements.
- Facilitating validation activities.
- Training and management of personnel.
- Approval of all working QC and production documents

1.2.2 Quality Assurance

The Quality Assurance is responsible for:

- Identifying and planning appropriate validation activities.
- Providing validation technical support and training.
- Ensuring appropriate validation procedures are in place.
1.2.3 Quality Control

The Quality Control is responsible for:
- Ensuring appropriate Quality Control (QC) procedures are in place.
- Identifying and planning appropriate validation activities for new products, test methods, and procedures.
- Provision and maintenance of auditable document storage systems.
- Approval of validation protocols for quality aspects.
- Maintenance of systems/equipment.
- Maintenance procedures.
- Calibration policy and procedures.

1.2.4 Buyer / Planner / Inventory Control / Label Department Supervisor

The Buyer / Planner / Inventory Control / Label Department Supervisor is responsible for:
- Identifying and planning appropriate validation activities for new suppliers, producers, and products.
- Maintenance of systems/equipment.
- Maintenance procedures

2.0 INTRODUCTION

2.1 Purposes of the VMP

The purposes of the VMP are to:
- Identify the members of the Validation Steering Committee.
- Identify applicable Regulatory requirements, to which Pharmco is adhering.
- Identify and describe the facility, systems and equipment that have to be validated.
- Identify and describe products and processes that have to be validated.
- Identify the validation activities that have to be undertaken.
- Identify the documentation requirements to support the above activities.
2.2 Overview of Project

This VMP relates to Pharmco Products Inc. facility located at 58 Vale Road, Brookfield, CT.

3.0 DESCRIPTION OF PRODUCTS AND PROCESSES

3.1 Introduction

Pharmco Products Manufactures a wide range of Pure Ethanol, Denatured Ethanol and High Purity Reagent Chemicals

This VMP applies to all production processes at Pharmco.

3.2 Product Groups

Products manufactured by Pharmco Products Inc. have been placed into several groups. A general process flow diagram (PFD) has been generated for each group.

Please refer to schedule of products, product group descriptions and associated process flow charts located in SOP 4-2-2 Quality Manual. Whenever new products are to be processed, then each will be assessed for inclusion into an existing group. Where this is inappropriate, e.g. a significant new process is introduced, then a new group will be added, with supporting PFD and process descriptions.

3.3 Processes

For each product group, the manufacturing processes and the specific equipment utilized are described in detail. Specifically, these include all processes critical to product quality. Processes that involve ‘standard’ operation of equipment, e.g. weighing of product materials, may be simply listed and referenced to appropriate equipment work instructions.

3.4 Product Storage and Distribution

Generally for compounded products, product storage time is relatively short, as most products are manufactured to meet customers’ orders. Products are stored within a dedicated storage area. There is a manual system for Inventory control.
4.0 EQUIPMENT AND SERVICES TO BE VALIDATED

4.1 Validation Status Spreadsheet (Form QA 357)

A comprehensive list of all the components critical to the product quality and therefore required to be validated has been generated. This spreadsheet will be updated as necessary through the life-cycle of the facility.

5.0 VALIDATION ACTIVITIES

Validation activities are carried out in accordance with this Validation Master Plan and the completed documentation is compiled into the Validation Files.

5.1.1 Validation Activities

All prospective and concurrent validation activities are performed according to previously agreed protocols. Any retrospective validation activities are comprised of a review and collation of existing data to demonstrate conformance to predetermined acceptance criteria. Details of the specific tests and methodology that are being used to determine validation compliance can be found in the validation protocols for each item. Validation protocols are included into the validation report for each item.

5.1.2 Installation Qualification

Installation Qualification (IQ) of items are carried out to ensure that as a minimum:

- The installation has been carried out according to specification and design intentions.
- A record of the principal features of the item and its components as installed is available.
- There is sufficient information available to enable the item to be operated and maintained safely, effectively and consistently.

5.1.3 Calibration

No validation study will commence without all equipment involved being verified to have been calibrated according to our SOPs and Work Instructions for the abovementioned equipment. For example, when validating filling equipment, balances used for determining fill levels must be calibrated prior to launch of the validation work.
Subject: Validation of Products & Processes and Validation Master Plan (VMP)

5.1.4 Operational Qualification

The Operational Qualification are carried out to determine as a minimum that:

- All critical instruments have been calibrated to allow subsequent validation work to be performed safely and with repeatable results.
- Each item of process equipment operates as specified throughout its anticipated operating range.

Before setting the item or system in motion, it is necessary to verify that:

- Equipment Operating Manuals are followed.
- Correct personal protection equipment and training in its use have been provided and documented.

5.1.5 Standard Operating Procedures or Work Instructions

Standard Operating Procedures (SOPs) or Work Instructions (WIs) must be in place to enable the items and systems to be operated consistently as intended during Performance Qualification testing. These may include, but are not limited to:

- Operation
- Cleaning
- Testing
- Sampling
- Maintenance
- Calibration
- Production processes
- QA/QC/Monitoring
- Training

5.1.6 Performance Qualification

Performance Qualification (PQ) test methodology encompasses testing as close as possible to production conditions. Performance Qualification has to determine whether the items, either in isolation or in combination with other items, can process defined standard loads or batches of a representative product consistently and repeatably to specification as defined in our IQ-
5.1.7 Process Validation

The purpose of process validation is to provide documented evidence that the process and facility can consistently produce product that complies with the appropriate Regulatory Standards and, if applicable, meets or exceeds previous recorded quality levels.

5.1.8 Cleaning Validation

Cleaning validation provides documented evidence that a cleaning procedure is effective in reducing, to pre-defined maximum allowable limits, all chemical contamination from an item of equipment or a manufacturing area following processing.

5.1.9 Analytical Method and Laboratory Equipment Validation

Analytical method validation and the associated laboratory equipment qualification have to provide documented evidence that test methods are effective, reproducible and repeatable. Validation of the analytical methods is a pre-requisite for any analytical testing associated with, for example, QC checks and cleaning validation assessments.

5.2 Validation Reports

At the end of any validation activity a validation report is completed. This report summarizes the results of the validation activity and highlights any issues such as deviations that have arisen.

5.3 Validation File

The Validation File contains all relevant documentation associated with the installation and operation of the facility, equipment and services. The documentation is held in the Quality Control / Document Control Department with controlled access. It is stored in an orderly manner, allowing prompt retrieval of any document.
6.0 CHANGE CONTROL

6.1 VMP Revisions

During the course of the facility validation lifecycle, this Validation Master Plan may be subject to amendment. Details of the amendments with reasons will be recorded in Revision History.

6.2 Definition of Change

Changes in the process and/or product should be evaluated to determine if revalidation is required. The objective is to minimize the quantity of documentation while retaining the audit trail of validation activities, for this reason the impact of proposed changes on the validation process has to be assessed. Generally, indications of significant changes will be, but are not limited to:

- Direct impact on product
- Changes required to test methods and/or acceptance criteria of protocols
- Test data in validation reports will require revision.

Changes that are likely to require revalidation are as follows:

- Changes in the actual process that may affect quality
- Negative trends in quality indicators
- Transfer of processes to another site
- Production area and support system changes
- Changes of packaging material

Changes of equipment which involve the replacement of equipment on a “like to like” basis would not normally require a revalidation.

6.3 Change Control Procedure

Every aspect of change control procedure for each department is described in detail in SOP 7-5-1-I Change Process Control.

All changes to production, equipment, test methods and such are submitted to the VP Quality Management on the Form QA 340 Pharmco Change Control Notification Form. After review, the criticality of the change is determined and either validation / re-validation is required.
7.0 QUALITY MANAGEMENT

Pharmco has elected to operate a quality management system (QMS) as required by the ISO 9001:2000 standard. This QMS will provide the basis for all SOPs that are utilized within the facility.

It is the responsibility of the QA/QC Department to assure the maintenance of ISO standards and applicable cGMP standards, as described by the VMP, for all processes associated with the manufacture of the products.

The VMP and associated documents will be updated as necessary to include any new product or process.

8.0 SCHEDULE OF STANDARD OPERATING PROCEDURES

It is a requirement of our ISO system that any component that contributes to the quality of our product must be controlled. Validation is a by-product of our quality program and another way of making sure that we are controlling our processes, equipment and methods properly.

As a part of our quality program a schedule of all standard operating procedures has been prepared and is being maintained to support the facility during its life cycle.

9.0 PREVENTATIVE MAINTENANCE

Pharmco Products Inc. is committed to ensure that effective preventative maintenance procedures are in place and are followed correctly as detailed in SOP 6-3-0-B Preventive Maintenance of Production and QC Equipment and WI IQ-OQ-PQ program for Critical Equipment. As a direct result of our IQ-OQ-PQ program, preventive maintenance schedule for all equipment and systems that have an impact on quality of the product has been established. This schedule is being maintained to support the facility during its life cycle.

10.0 TRAINING

Pharmco Products, Inc. has created a wide-ranging program for the training of personnel as described in SOP 6-2-2-J Training Effectiveness and Verification. This program ensures that:

- The appropriate level of training and education is provided for all personnel employed within the facility.
- Training effectiveness is verified.
Training records are established and maintained for all personnel employed within the facility.

11.0 RESPONSIBILITIES AND APPROVAL OF PROTOCOLS AND DOCUMENTATION

Validation protocols / reports are reviewed by the members of Validation Steering Committee and signed upon approval by the Vice President of Quality Management.

<table>
<thead>
<tr>
<th>Revision #</th>
<th>Revision Date</th>
<th>Revised by</th>
<th>Reason for Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EF</td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td>10/7/05</td>
<td>PD/EF</td>
<td>SOP is updated in light of the progress made in the program since it’s inception.</td>
</tr>
</tbody>
</table>

This printed document was printed on: 3/12/2007. This printed document is valid for 5 days after the print date. All obsolete documents must be appropriately marked or discarded.