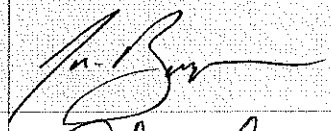
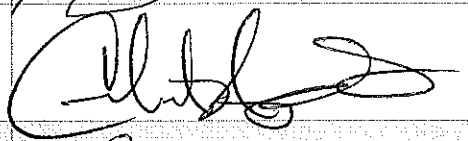
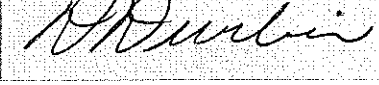
Approval

The signatures listed below certify that all items in this Master Plan have been reviewed and found to be acceptable. The approval of this Master Plan is the responsibility of the listed functional areas of Giles Chemical, Co.

Representative	Functional Area	Signature	Date
Patrick Owen	Engineering		4/26/17
Kenneth Basehore	Engineering		4/26/17
Jason Bumgarner	Production		4-26-17
Matt Haynes	Operations		4-26-17
Deborah Durbin	Quality		4-26-17

Contents

1.0 Introduction

1.1 General

Giles Chemical manufactures USP grade Magnesium Sulfate ($MgSO_4$) also known as Epsom Salt in a continuous process. This product is considered an Active Pharmaceutical Ingredient (API) and is also sold as an over the counter (OTC) product. In addition, some product sold as industrial grade bulk chemicals. All production is intended to meet current Good Manufacturing Practice (cGMP) guidelines for API's.

This Validation Master Plan (VMP) outlines the general validation program to be used for the entire facility. This document will be amended for the addition of any new product or equipment or change in class of production areas. These addenda will then describe the specific validation program that will be used for each of the products or processes associated with that area.

The FDA defines validation as "establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes". Validation has also been defined as the activity performed to demonstrate that a given utility, system, process or piece of equipment does what it purports to do. The primary means of accomplishing this end is a documented scientific study designed to specifically permit the determination as to whether the entity under scrutiny in fact:

- Meets or exceeds the specifications of its design
- Is properly built, installed, operated and maintained
- Is suitable for its intended application
- Conforms to basic CGMP design and operation criteria
- Will satisfy the concerns of regulatory agencies
- Is capable of consistently producing a product that meets all pre-determined specifications and quality attributes
- Will meet the goals established for productivity, safety and quality

The Validation effort will be supported by at least the following existing standard operation procedures (SOPs):

- Approval and Release
- Change Control
- Preventative Maintenance and Calibration
- Documentation
- Incidence Investigation
- Internal Audit
- Training

1.2 Validation of Process Support Systems

The validation of all systems, equipment, facilities, and testing methods are regarded as prerequisites in the validation of a manufacturing process.

In addition:

- Critical Utilities Systems that directly impact the quality of a product, shall be validated. Non-critical utilities are to be handled according to Good Engineering Practices and will be documented through the commissioning process.

2.0 Scope

The scope of this document is to describe Giles Chemical policies and general validation procedures for manufacturing and support processes and systems located at the Waynesville, NC site. The policy of Giles Chemical is to conform to all US, EU and world cGMP requirements that are associated with the production of API, OTC, and bulk chemical products.

One purpose of this Validation Master Plan is to serve as a liaison document between Giles Chemical and the FDA. It conveys Giles Chemicals' understanding of company responsibilities concerning the validation and certification of the facility, along with plans to discharge that responsibility. Another purpose of this Validation Master Plan is to provide an outline and description of related validation programs and protocols necessary to qualify Giles Chemical's facility in Waynesville, NC

Individual protocols that will be prepared for this facility supersede any criteria or specifications in this document.

This master plan will be reviewed annually and updated as necessary. Addendum or additional Validation Master Plans will be prepared as indicated above for any additional products added to the production schedule.

3.0 Facility and Process Description

3.1 Facility Description

Giles Chemical's USP Epsom Salt process in located in the plant at 102 Commerce Street in Waynesville, NC. The facility is a metal and concrete block building approximately 300 feet long by 100 feet wide adjacent to the banks of Richland Creek. The raw material storage area is across the creek and consists of two 30,000 gallon acid tanks in a containment dike and three 100 ton silos for MgO storage.

The facility in Waynesville, NC is divided into eight (8) major areas. These are:

- Raw Material Receiving/Storage
- Digesters
- Filter Press
- Crystallizers
- Dryers
- Packaging
- Warehouse Area
- Lab Services (QC)

3.2 Process Description

The Magnesium Oxide (MgO) and Sulfuric Acid (H_2SO_4) are unloaded from railcars into the MgO Silos and the Acid Storage Tanks.

The MgO and H_2SO_4 are combined with water and mother liquor (Brine that has had Crystals removed from it) in the Digesters. The pH and specific gravity are critical parameters and are controlled in the Primary Digesters. The material, referred to as "mud" after the Primary Digesters overflows into Secondary Digesters which allow for more reaction time. The Secondary Digesters overflow into the Mud Tanks which are surge tanks for the Filter Presses.

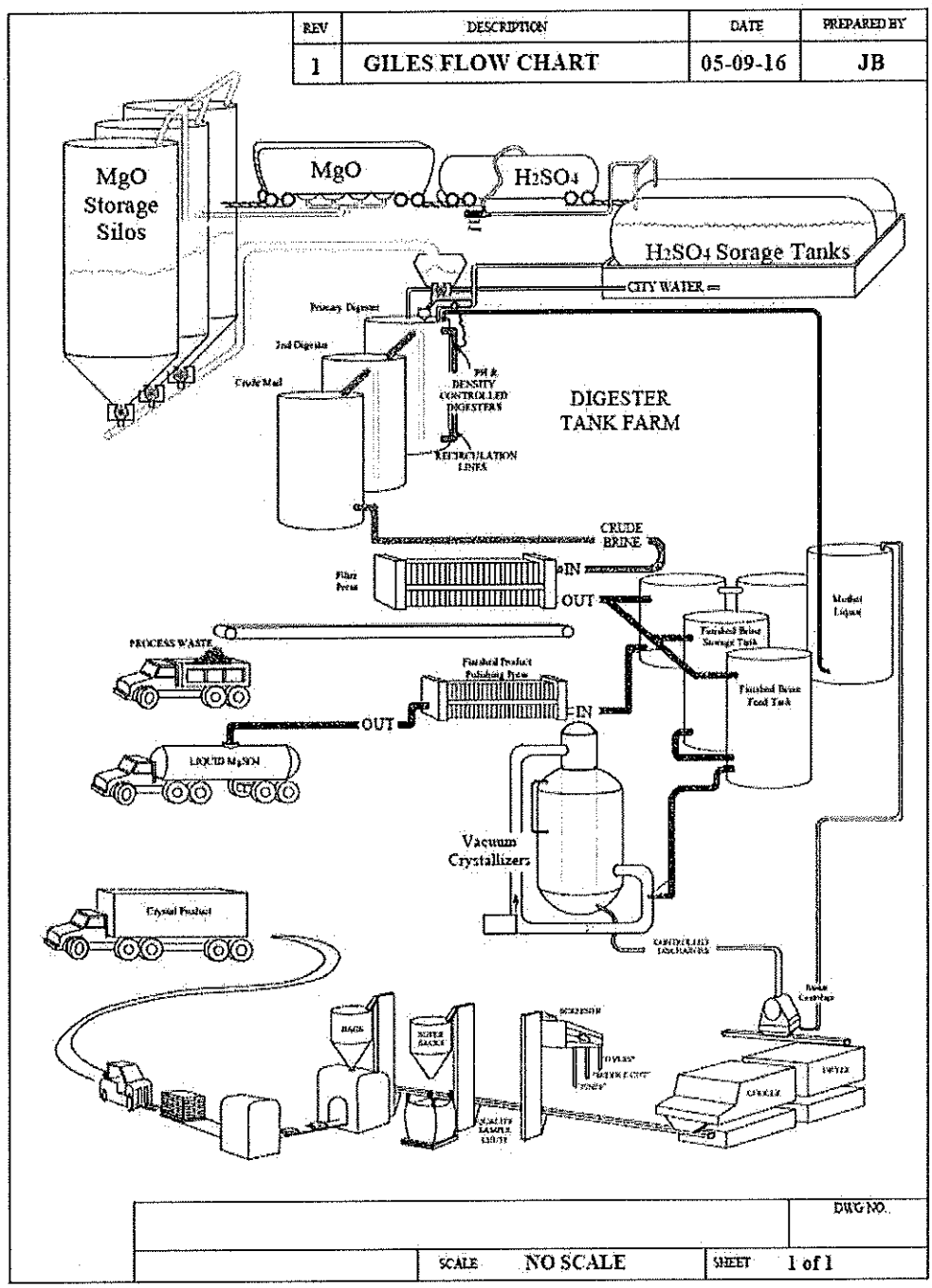
The Filter Presses remove contaminants from the mud, such as sand, other silicates, unreacted MgO, calcium sulfate, and other non-dissolved contaminants from the mud. The waste material is removed from the Filter Presses at intervals determined by the flow going through them. When the flow coming out is significantly less than the Brine being consumed by the Crystallizers, another Press is started and the "slow" press is stopped and the material removed. The "mudcake" is landfilled.

After the Filter Presses the liquid is referred to as "brine". The critical parameters for Brine are the specific gravity and clarity. The Digesters control the specific gravity and the Filter Presses determine the clarity. If the material is not clear, it can be cycled back through the Filter Presses.

From the Filter Press, the brine goes to surge tanks that feed the Crystallizers. In the Crystallizers, crystals of Magnesium Sulfate Heptahydrate are formed and grown. This process operates continuously. The Crystallizers operate by evaporative cooling. The critical parameter for Crystal production is temperature. The temperature is controlled in the Crystallizers by controlling the vacuum applied. The output from the Crystallizers is fed to Centrifuges which separate the supernatant (referred to as mother liquor) from the wet Epsom Salt crystals.

The Dryers receive the wet Epsom Salt Crystals, dry them with indirectly heated air and cool them with indirectly cooled air. The critical parameter for the Dryers is the surface moisture of the salt. This is controlled indirectly by controlling the temperature of the air used to dry the salt.

The dry Epsom Salt is then packaged into either "Super Sacks" or 50 pound plastic bags and sent to the Warehouse area for approval and shipping.



4.0 Validation Approach

The purpose of this section is to provide an explanation of the validation plan for the entire Giles Chemical Facility. This document provides an overview of the basic approach that will be used to complete the validation program.

Where feasible, validation methodology will employ those techniques widely accepted by the scientific community such as the PDA Monographs and Technical Reports, ICH Guidelines and ISPE baseline guides as well as all FDA regulations and guidelines.

Representatives from Quality Assurance and Operations will review all validation documents. They will review and approve those areas, as appropriate, based on their knowledge and experience. Others may be called on for review and approval of specific protocols depending on their experience and/or expertise. Upon completion of protocol implementation, these representatives, who pre-approved and signed this document, will review and sign acceptance of the completed validation effort.

The prospective approach is the preferred method of validation however, due to the nature and activity of the business and the fact that the products currently manufactured here have been established for many years, this will be combined with a retrospective and or concurrent approach. The retrospective validation, for existing process equipment, if used, will not be used alone, but may be incorporated into the prospective method to supplement the data when the process has been in use for a period of time.

Prospective Validation is that carried out on a "pre-planned" basis before a process is put into routine production. All processes shall undergo prospective validation, however as noted above, retrospective data may be used.

Retrospective Validation is validation based on the review and analysis of historical data obtained from recent and past manufacture of the product. Retrospective validation and Annual Product Evaluation Review are not acceptable substitutes for prospective/concurrent validation. Thus, it shall be used only as background information, supplemental material for prospective or

concurrent validation and a temporary documentation pending prospective validation as stated above. Exceptions to these requirements shall require prior authorization from QA/QC management.

The need to revalidate or re-qualify will be assessed on a triannual basis so as to assure continued cGMP compliance. Typically, a decision to re-validate shall be triggered by a review of the product over a long term (e.g., Annual Product Evaluation Review). Alternatively, there is an indication of a need for a re-assurance that the materials and/or process are still in the state of control. This may be caused by several small changes made during the course of a year. Each of these changes may not, by themselves, trigger the re-qualification program; however, the cumulative change will require re-qualification of the component or system.

4.1 Systems Approach

A "Systems Approach" to this validation program will be employed during the course of the Giles Chemical facility validation. This "Systems Approach" will be such that all equipment ancillary and peripheral to the central devices will be included in the certification packages. For example, the qualification of pumps will be joined with the qualification of the major equipment it is serving.

This approach will achieve the desired end of attaining an integrated package with each piece of equipment qualified in the context of its actual intended end use. This approach also serves to avoid the pitfall of accidental omission of qualifications that are mandatory.

Validation or Qualification tasks must be completed in a precise order. For example, the Installation Qualification (IQ) protocol execution needs to be completed prior to starting the Operational Qualification (OQ) protocol execution. Exceptions are possible, where execution of a protocol does not need or interfere with the preceding protocol and with the prior approval of the Quality Unit. However, completion, that is signature approval, must be performed in order. The order of validation is IQ, OQ, and Performance Qualification (PQ). Utility systems or components that are relied on for other equipment or system operation must be fully validated or qualified prior to the equipment dependent on its operation. In some cases validation protocols may be generated and/or executed simultaneously

In order to achieve the high degree of assurance required by the definition of the term "validation", multiple repetitions or observations of each study are usually required. In general, a minimum of three repetitions is an accepted standard, although in some cases testing or monitoring over a considerably longer period of time is indicated (such as in the extended monitoring of a Compressed Air System) in order to account for all variable process conditions. In such cases, a single test will be defined as a cycle sufficiently long in duration so as to contain all of the various operations that may be involved at least once. For such systems, it is highly probable that some type of ongoing monitoring at decreased intensity will be required on a continuous basis and will satisfy much if not all of the revalidation requirements.

In some instances, a single confirmation or verification will be sufficient (such as in the evaluation of an operational SOP or in the inspection of materials of construction). In all cases, the methodologies and frequencies to be followed will be contained in the validation protocols.

The test design for all validation studies will attempt to evaluate the performance of the system or equipment being tested under a range of operating parameters representing the actual intended use conditions.

All studies performed will be adequately documented. The documentation required by each protocol will be assembled into a permanent validation file. Designated individuals with appropriate experience, education or training will review the validation files and evaluate the data.

Whenever possible, raw data and calculated results will be presented or referenced in preference to a "pass", "fail", or "no-test" (or equivalent terms) disposition for each study according to stated acceptance criteria. When multiple tests are required, there must be consecutive successful runs resulting in a "Pass" disposition that will be required to constitute a validated state. A failure of any one of the trials will automatically disqualify the other trials.

Any failing studies will be the subject of a documented investigation as to its cause and to determine an appropriate corrective action. It is expected that corrective action will be initiated and completed before a new series of validation trials is begun. Studies that are disqualified for technical reasons, such as lab accidents or equipment breakdowns, not related to or due to the test or process being tested, will be considered as "no-tests". Such studies will have to be repeated but will not usually require a documented investigation (beyond a justification/explanation of the "no-test" finding) and do not disqualify any acceptable test runs previously achieved. All studies performed, regardless of final disposition, will be retained as part of the permanent validation file.

The successful completion of a validation study qualifies specific equipment and/or processes, following specific procedures, for use in a specific application. In order to maintain that equipment and/or process in a "validated state", supporting systems and programs (as described below in Section 10 of this Validation Master Plan) are necessary to avoid changes in the characteristics or capabilities of the equipment/process, which would invalidate the original results. In all circumstances, the absence of appropriate documentation of activities is equivalent absence of the activity itself.

4.2 Approval for Rework

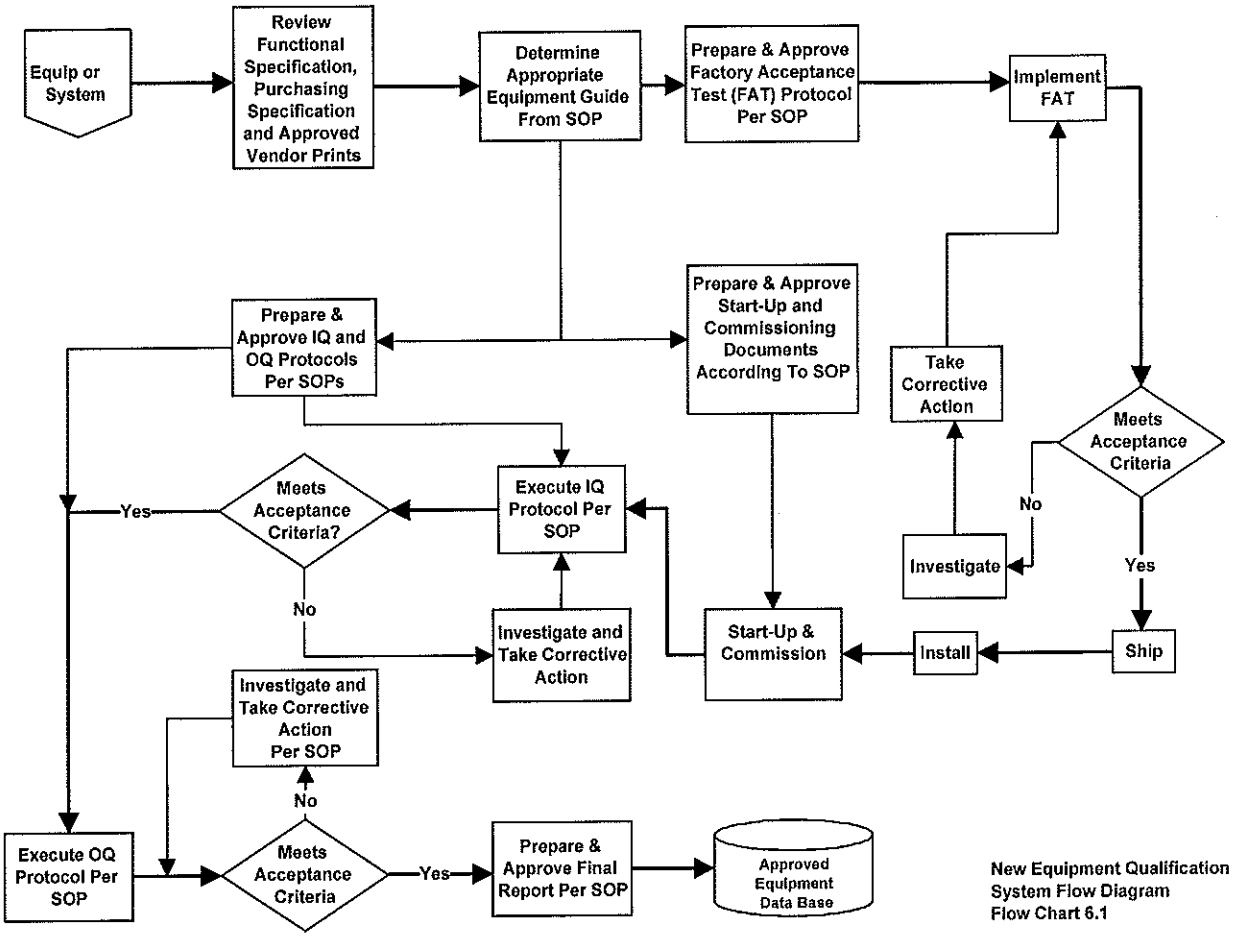
By definition, the consideration and decision making procedures for Rework shall be subject to the site's procedures for managing Process Deviations/Discrepancies.

4.3 Shipping Conditions

Under appropriately designed protocols, studies shall be conducted and documented to prove that the shipping conditions to which the goods are exposed are consistent with the prescribed storage conditions on the product label.

4.4 Validation Flow Chart

The following process flow chart depicts the generally accepted approach for New Equipment. Additions will be validated according to needs specific to that piece of equipment and its intended use.



New Equipment Qualification System Flow Diagram Flow Chart 6.1

5.0 Responsibilities

As indicated above the Validation Master Plan will be reviewed and approved by responsible Giles Chemical personnel prior to implementation of the validation program. Among those individuals responsible for the review and approval of this Master Plan include:

- Director of Operations
  - Manage business objectives
  - Oversee all aspects of Manufacturing

- Quality Assurance
    - Analytical testing
    - CGMP Activities
    - Inventory Control
- Process Engineer
    - Establish and write SOP's and Training
    - Evaluate statistical process data
- Production Manager
    - Daily Operation of the facility
    - Oversee warehousing

Some functions or tasks, listed below, may not apply to Giles Chemical as based upon their current operation. These are included so as to allow for changes in the future.

Primary (P): Means that that group is responsible for assuring that all aspects of the task are complete and documented. They can assign specific tasks to others as necessary in order to complete their function.

Secondary (S): Means that this group will be available to assist the primary assignee to facilitate the completion of the required task.

None (N): Means that no direct or implied responsibilities are intended for that group or function.

The groups listed in this table are those team members with overall responsibility to assure that if necessary the task is completed.

Function	*Quality*	*Operations*	*Engineering*	*Comments*
Validation Master Plan				
Prepare Draft	S	N	P	
Review	S	S	P	
Edit and Revise	S	N	P	
Validation Protocols				
Format	P	P	P	Jointly Developed

Develop Acceptance Criteria	S	P	P	Based on Operating Conditions
Prepare IQ Draft	S	N	P	
Prepare OQ Draft	S	N	P	
Prepare PQ Draft	S	N	P	
Review and Approve	P	P	S	
Edit and Revise	S	N	P	
Execute IQ	N	S	P	
Execute OQ	N	S	P	
Execute PQ	N	S	P	
Calibration	N	P	P	
Issue Final Report	S	N	P	
Passivation	N/A	N/A	N/A	Not currently needed
Drawing/Document Management				
P&IDs	N	N	P	
Shop Drawings	N	N	P	
As Built Drawings	N	S	P	
Prepare Equip. Files	N	S	P	
Maintain Equip. Files	N	S	P	
cGMP Training	P	S	S	
Analytical Testing	P	N	N	
Validation Programs				
Preventative Maintenance	S	P	S	
Change Control	S	P	S	
Methods Validation	P	S	N	
Annual Reports	P	N	N	
Document Control	P	N	N	
Training	S	P	S	

6.0 Protocols

This section will outline the various types of validation protocols. It will also list expected protocols for each section of the plant.

6.1 Installation Qualification (IQ)

The installation qualification (IQ) documents the physical attributes of the equipment or system. It contains construction documentation such as Material of Construction certifications, Pressure Test Reports, size, etc. It also contains control systems documentation (if necessary). It retains engineering and construction documents such as Process and Instrumentation diagrams (P&IDs), vendor information, and drawings for system components, installation verification and testing are referenced for future use and to facilitate the Operational Qualification.

The information in the IQ package provides field verification that the equipment specified is installed in accordance with Giles Chemical' specifications for use, and/or manufacturer's recommendations. It verifies that pre-approval installation and test procedures have been satisfactorily conducted prior to system acceptance by Giles Chemical. A system description consisting of the following installation information will be included and verified as part of the IQ (where and as appropriate):

- Manufacturer, serial number, model number capacities of major equipment
- Materials of construction
- Installation certification of piping and other system components
- Critical and non-critical instrumentation identification.
- List of software and hardware
- Drawing(s) showing system components and connections
- Utility Equipment

IQ package documents are checked for completeness, referenced within other validation documents and constitute an integral part of the total validation package.

6.1.1 General IQ Acceptance Criteria

- Systems and equipment are installed in compliance with approved engineering drawings and documents
- Applicable design documentation is available for review. This may include:
  - Process and Utility Flow Diagrams
  - Engineering/Piping and Instrumentation Diagrams (P&IDs)
  - Equipment and Installation Specifications
  - Software Testing Reports
  - Equipment and instrumentation vendor, model, capacity, material and other critical features are verified as correct against approved engineering specifications.
  - Electrical wiring is completed in accordance with design specifications and loops are verified per installation specifications
  - Instruments are calibrated according to approved procedures and traceable to National Institute of Standards & Technology (NIST) standards or other reproducible standards, where applicable.
  - Motors, and pumps are verified to assure correct electrical requirements. Manufacturer, model number and capacity is also verified. Nameplate data is recorded to provide information and assurance of correctness of size.
  - Piping systems are flushed and cleaned per approved procedure to remove dirt and debris. Hydrostatic testing is often completed during the IQ testing. Cleaning procedures are documented. Piping installation records are available for inspection. Testing and verification meet or exceed industry standards for welding, welder and machine qualifications.
  - Pressure and/or vacuum piping and equipment are tested per approved procedure and certified. Test records and appropriate certifications are available in the IQ.
  - The utility supply requirements meet the design specifications.

6.2 Operational Qualification (OQ)

The Operational Qualification documents that the equipment and systems used at Giles Chemical operate as specified and meet pre-approved design requirements for control of operating parameters. OQ testing is designed to simulate full operating conditions to establish a performance baseline that will make sure that the challenged system operates as intended, and as a system check in the event of malfunction. For each system or piece of equipment requiring OQ testing, alarm interlock and timer/clock testing will be conducted as part of the OQ requirements. Specific acceptance criteria will be stated in each validation protocol.

If appropriate, vendor audit, design review (structured walk-through), testing and functional test reports and software test logs are reviewed and approved.

6.2.1 OQ Acceptance Criteria

- Required testing is conducted in accordance with pre-approved protocols and applicable procedures.
- Automated control sequences (associated with systems/equipment to be validated) including but not limited to interlocks, alarms and timers shall function in accordance with the approved design.
- Automated system hardware and software functions under expected environmental conditions without undesirable results.
- Indicating and recording instruments utilized to obtain test data required by system/equipment protocols are calibrated according to approved procedures, within calibration period, pre- and post- calibrated where appropriate and traceable to NIST, or other reproducible standards where applicable. (Note: If not done in IQ)
- Draft (or preliminary) Standard Operating Procedures (SOPs) prepared and are reviewed.
- Mechanical equipment such as pumps, motors and agitators operate as designed. This may include output capacity, rotation and current draw. Pumps and related equipment are checked for correct "no load" operation by

determining their direction of rotation, speed control, etc. and under "load" conditions, where the units are checked for range of operation speed and volumes, ability to maintain operation for required time and more.

- SOPs for automated controlled systems are checked to verify implementation of adequate change control for hardware and software.
- Controller variables shall confirm the design specifications.
- All other acceptance criteria in the protocol.

6.3 Performance Qualification (PQ)

The Performance Qualification is a pre-approved testing program required to verify acceptable performance of critical utility systems and process equipment items such as weighing, temperature, and level measuring equipment, and compressed air. During performance qualification, systems may be challenged throughout proposed operating ranges during extended periods to verify system operating capabilities under presumed "worst case" conditions. Specific acceptance criteria will be stated in each corresponding validation protocol.

6.3.1 PQ Acceptance Criteria

- Required testing is conducted in accordance with approved protocols and applicable procedures.
- Instrumentation used to acquire test data required by the protocols are calibrated according to approved procedures, within calibration period, pre-and-post calibrated, where appropriate, and are traceable to NIST or other reproducible standards where applicable.
- The system performance as defined by appropriate tests and Acceptance Criteria, reliably and consistently meets the performance specifications under conditions of actual intended use.

6.4 Final Reports (Summary Reports)

The Final Report summarizes the validation test results and provides an analysis of the test data and a conclusion about the ability of the equipment, system, and process to consistently perform within acceptable operating ranges and production materials meeting established specifications. Deviations and/or exceptions to approved validation test procedures along with suitable explanations are also documented and explained in the final report.

A final report summarizing the results of the IQ/OQ/PQ process shall be prepared, noting the following:

- Protocol deviation reports that were generated, including the rationale for resolving the deviations and corrective actions that were taken to resolve the deviations, shall be included in the final report.
- References to the calibration and maintenance procedures that will be used by the laboratory to perform periodic calibrations and maintenance of the system shall be included in the final report.
- The final report shall be reviewed and approved in accordance with an approved SOP. Review and approval of all qualification protocols shall be performed in this report.
- The final report and all data shall be archived in the Instrument File on the shared drives
- Following an equipment/instrument qualification, the Qualification Project Plan shall be updated and included in the site Master Validation Plan.
- Following qualification, change control criteria should be developed for re-qualification of equipment/instruments after a major repair, upgrade or relocation.
- Copy of the unexecuted approved protocols

6.5 Expected Protocol List

Functional Area	*IQ*	*OQ*	*PQ*
Raw Material Storage	No	No	No
Filter Press	Yes	Yes	Yes
Crystallizer	Yes	Yes	Yes
Dryer	Yes	Yes	Yes
Super Sack Packaging	Yes	Yes	No
50# Bag Packaging	Yes	Yes	No
Warehousing	No	No	No
QC Balances	Yes	Yes	No
QC pH Meter	Yes	Yes	No
Compressed Air	Yes	Yes	No
Boiler/steam	Yes	No	No

6.6 Acceptance Criteria

6.6.1 General

All equipment will meet the design and functional specifications established by Giles Chemical. The specific qualification protocols, as described above, will provide specific criteria that will be met prior to determining equipment acceptance. The general acceptance criteria are:

- Meets vendor and Giles Chemical specifications for operation and installation
- All computer or PLC controlled devices will pass RFI and EMI tests using standard sources for such interference, e.g., security radios, and electric drills
- Meets all functional specifications per production requirements as established by Giles Chemical

- There are no leaks in piping or tanks
- Tanks will hold required volume of liquid and at the specified temperature

6.6.2 Specific Areas

Functional Area	*IQ*	*OQ*	*PQ*
Digesters	Vessel is level	Direction of rotation is specified	Raw material delivery operates acceptably
	Access for operation is acceptable	Utilities are connected according to specification	pH control keeps output in range
	Materials of construction are acceptable	Hatch does not leak	Specific gravity control keeps output in range
		Circulation loop is functional	
		Washouts are operable	

Filter Press	Unit is installed according to specifications	Squeeze pressure is appropriate	Brine clarity meets needs of crystallization
	Materials of construction are acceptable	Associated pumps work properly	
	Access for operation is acceptable	Associated pumps have correct rotation	
		Cloths do not have creases or folds	
Crystallizer and Centrifuge	Unit is installed according to specifications	Unit will pull and hold a pressure of < 1.2" Hg	Crystal size meets specification
	Materials of construction are acceptable	Circulation is acceptable	Temperature control will hold correct setpoint
	Access for operation is acceptable	Vacuum and temperature controls are functional	Centrifuge ouput will meet dryer specification
		Pumps have proper rotation	

		Centrifuge has proper rotation	
		Centrifuge runs at appropriate speed	
Fluidized Bed and Cooler	Unit is installed according to specifications	Air flows meet requirements for salt flow	
	Materials of construction are acceptable	Heat controls are functional	
	Access for operation is acceptable	Blowers turn in correct direction	
		Vacuum gages are installed correctly	
		Vibration is of the correct amplitude and angle	
Super Sack Packaging	Unit is installed according to specifications	Output is capable of weighing supersacks in the correct weight range	

	Access for operation is acceptable	Shutoffs and relays are working correctly	
	Scales are not preloaded	Air inflator is operating correctly	
Bag Packaging	Unit is installed according to specifications	Output is capable of weighing supersacks in the correct weight range	
	Access for operation is acceptable	Shutoffs and relays are working correctly	
	Scales are not preloaded		
Compressed Air	Unit is installed according to specifications	Pressure meets specifications	
	Access for operation is acceptable		
Boiler	Unit is installed according to specifications		

	Access for operation is acceptable		
pH Meter	Unit is installed according to specifications	Unit is calibrated	
	Materials of construction are acceptable	Accuracy is appropriate for use	
	Access for operation is acceptable		
Balances	Unit is installed according to specifications	Unit is calibrated	
	Access for operation is acceptable	Accuracy is appropriate for use	

7.0 Documents

All protocols, will be reviewed by a matrix of responsible individuals chosen on the basis of their knowledge of the system and for their education to provide comments and/or edits

Upon completion of a system, qualification/validation, the respective IQ, OQ, and PQ, protocols will be electronically preserved where ease of retrieval is possible and raw data is preserved along

with the corresponding final validation summary report. Giles Chemical retains the total package in a secure documentation storage location.

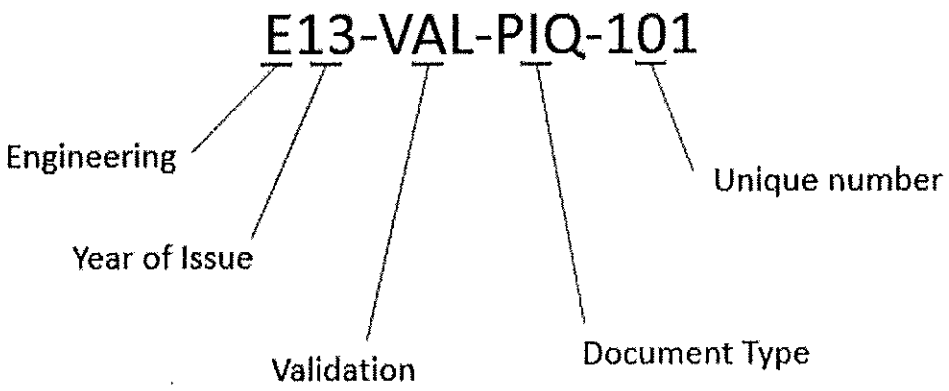
7.1 Validation Document Control

The coordination, distribution and control of documents at the Giles Chemical, Facility in Waynesville, NC, will be a centralized activity according to their document control procedures and under the authority of the Quality Department. The validation documents to be controlled at Giles Chemical will include, but not necessarily be limited to, validation protocols, standard operating procedures, validation reports and analytical methods. The Quality Department will maintain all original documents. These originals will be considered original only when final sign off has been performed by QA/QC. Other documents will be stamped "For Information Only", "Uncontrolled", or "Desk Copy" as appropriate. Reproduction and distribution of controlled copies will be the responsibility of the Quality Assurance department. Prior to distribution, all controlled documents will be assigned an effective date, this date will be the date of final approval by the QA/QC unit. Signed originals will be maintained in a historical file.

7.2 Validation Documents and Numbering System

Validation documents are indexed or uniquely identified.

- Document Type – The document types are as follows:
  - IQ – Installation Qualification
  - OQ – Operational Qualification
  - PQ – Performance Qualification
  - FR – Final Report
  - CV – Cleaning Validation
  - PV – Process Validation
  - VP – Validation Plan
- Numbering System – All documents related to the validation program will be numbered according to the following scheme:



- The unique numbers follow this format for the 'hundreds' digit:
  - 000 – General
  - 100 – Raw Materials
  - 200 – Digesters and Press
  - 300 – Crystallizers and Centrifuge
  - 400 – Drying Systems
  - 500 – Packaging Systems
  - 600 – Utilities

7.3 Required or Expected Documents

The following lists provide guidance as to the documents that are normally required for a full validation effort. In some cases, some of the documents are not available, or may not exist at all. These lists can be adjusted as necessary to accommodate each system.

7.3.1 SOPs for Process Equipment

SOP	*Digester*	*Filter Press*	*Crystallizer*	*Dryer/Cooler*	*Super Sacker*	*Bagger*
Operation	Yes	Yes	Yes	Yes	Yes	Yes
Preventative Maint.	Yes	Yes	Yes	Yes	Yes	Yes
Cleaning	No	No	No	No	No	No
Safety	Yes	Yes	Yes	Yes	Yes	Yes
Emergency	Yes	Yes	Yes	Yes	No	No
Change Control	Yes	Yes	Yes	Yes	No	No
Training	Yes	Yes	Yes	Yes	Yes	Yes
Calibration	No	No	No	No	Yes	Yes
Re-Qualificaiton	Yes	Yes	Yes	Yes	Yes	Yes
Annual Review	Yes	Yes	Yes	Yes	Yes	Yes

7.3.2 SOPs for Utilities

SOP	*Air Compressor*	*Boiler*
Operation	Yes	Yes
Preventative Maint.	Yes	Yes
Cleaning	No	No
Safety	Yes	Yes
Emergency	Yes	Yes
Back Up	No	No
Security	No	No
Change Control	Yes	Yes
Training	Yes	Yes
Calibration	No	No
Re-Qualificaiton	Yes	Yes
Annual Review	Yes	Yes

7.3.3 SOPs for the Laboratory

SOP	*Balances*	*pH Meter*
Operation	Yes	Yes
Preventative Maint.	No	Yes
Cleaning	No	No
Safety	Yes	Yes
Emergency	No	No
Back Up	No	No
Security	Yes	No
Change Control	No	Yes
Training	Yes	Yes
Calibration	Yes	Yes
Re-Qualificalton	Yes	Yes
Annual Review	Yes	Yes

7.3.4 Expected Documents

Document	*Digester*	*Filter Press*	*Crystallizer*	*Dryer*	*Super Sacker*	*Bagger*
P&ID	Yes	Yes	Yes	Yes	No	No
PFD	Yes	Yes	Yes	Yes	No	No
Isometrics*	No	No	No	No	No	No
Operations Manual	No	Yes	No	Yes	Yes	Yes
Preventative Maint.	No	Yes	No	Yes	No	No
Cleaning Manual	No	No	No	Yes	No	No
Passivation Report	No	No	No	No	No	No
Weld Certification	No	No	No	No	No	No
Hydrostatic Report	No	No	No	No	No	No
Leak Test Report	No	No	No	No	No	No
ASME Certification	No	No	No	No	No	No
Mill Report	No	No	No	No	No	No
Calibration Certification	No	No	No	No	Yes	Yes

* *Water Only*

8.0 Control System Description

The control systems installed at this facility are simple direct control dedicated to the specific piece of equipment. Therefore, it is not intended to do a full computer validation program for these controllers at this time. A basic test and review of structural characteristics will be performed. All testing will be on a functional basis. However, as stated earlier, this document will also serve as a general guideline for the addition of other equipment that may require more extensive validation.

Where specific protocols are to be developed, the following will guide the development of the documents.

8.1 Installation Qualification (IQ)

The IQ document will include the design documentation such as functional requirement specification, control system vendor audit, software functional requirements, software development procedures, change control documentation, system operating manual, vendor supplied manuals, and design documentation. The IQ will also include following specific verification:

- List and location of the following documents; design specifications, purchase orders, shop drawings, loop drawings, configuration drawings, system architecture drawings, Input/Output (I/O) listings, terminal and wiring diagrams, field devices/instrumentation listings, and spare parts lists.
- Wiring and cabling is correct, i.e., wires and cables originate at proper Input/Output (I/O) rack locations and terminate at the correct device (display, power supply, etc.) or instrument.
- Electrical continuity verification for wiring and cabling.
- Hardware switch setting, and jumper positions are in accordance with design specifications and vendor instructions.
- Site installation and qualification including electrical grounding.

Where appropriate, software installation documentation will provide the detail necessary to allow for restoration of the software to an operational state following a functional loss. Automation hardware verification will be based upon both manufacturer requirements and engineering specifications.

These may include loop check records, but will not duplicate otherwise satisfactorily documented testing of hardware termination's and interconnections.

8.2 Operational Qualification (OQ)

The OQ will verify that software is installed correctly, and controls and monitors a process in accordance with applicable functional specifications. OQ verification will confirm that system hardware also operates properly. Specific OQ will include:

- Testing of security level to prevent unauthorized changes to software.
- Verification that archived or master copies of applications software are identical to software residing on system hard drives or other storage devices.
- Power loss testing to verify that, in the event of power failure, a computerized system, including any application program, recovers without loss of data or system integrity.
- Functional testing of software where specific inputs are entered at logic gates and the corresponding output is observed and compared to the system functional specification and/or logic flow diagram.
- Verification of the display (as possible) and operator interface requirements (provided by system supplier).
- Critical alarm listing and test results.

If required, software structural testing records are verified to assure quality software design methodology.

8.3 Performance Qualification (PQ)

Performance Qualification of the computerized control system will verify that the integrated system operates correctly during production conditions. The PQ will verify that alarms are properly logged, data is compiled and manipulated, and control is maintained over the corresponding piece of process equipment or utility system.

8.4 Part 11

The need for compliance with Part 11 will be undertaken as part of the qualification process. A checklist will be used to evaluate the need for implementing Part 11 validation. If it is found to be needed a qualification protocol will be prepared and the system brought into compliance. In addition, and SOP will also be prepared to maintain the system in full compliance of Part 11 regulations.

9.0 Project Schedule

The following schedule demonstrates how the validation activities for Giles Chemical Facility will be implemented.

	IQ Complete	*OQ Complete*	*PQ Complete*	*Final Report Complete*
Crystallizer #4	Aug-13	Aug-13	Aug-13	Aug-13
Cleaning Validation	Feb-15	Feb-15	Feb-15	Mar-15
Crystallizer #5	Mar-15	Mar-15	Mar-15	Apr-15
Crystallizer #6	Jan-16	Jan-16	Jan-16	Jan-16
Dryer and Cooler	Feb-16	Feb-16	Feb-16	Mar-16
Bagger	Nov-16	Nov-16	Nov-16	Nov-16
Main MgO Mix Pot	Jan-17	Jan-17	Jan-17	Feb-17
Digester #4	Feb-17	Feb-17	Feb-17	Mar-17
Netzsch Press	Mar-17	Mar-17	Mar-17	Apr-17
Digester #1	May-17	May-17	May-17	Jun-17
Digester #2	May-17	May-17	May-17	Jun-17
Digester #3	Jun-17	Jun-17	Jun-17	Jul-17
ACS Press	Jun-17	Jun-17	Jun-17	Jul-17
Komline Press	Jul-17	Jul-17	Jul-17	Aug-17

Eimco Press	Jul-17	Jul-17	Jul-17	Aug-17
Crystallizer #1	Aug-17	Aug-17	Aug-17	Sep-17
Crystallizer #2	Aug-17	Aug-17	Aug-17	Sep-17
Crystallizer #3	Sep-17	Sep-17	Sep-17	Oct-17
Large Centrifuge	Sep-17	Sep-17	Sep-17	Oct-17
Small Centrifuge	Sep-17	Sep-17	Sep-17	Oct-17
Super Sacker	Oct-17	Oct-17	Oct-17	Nov-17
Air Compressor	Nov-17	Nov-17	Nov-17	Dec-17
Boiler	Nov-17	Nov-17	Nov-17	Dec-17
Balance - Lab	Nov-17	Nov-17	Nov-17	Dec-17
pH Meter - Lab	Nov-17	Nov-17	Nov-17	Dec-17
Process Validation	Dec-17	Dec-17	Dec-17	Jan-18
Part 11 Validations	Dec-17	Dec-17	Dec-17	Jan-18

10.0 Reference Documents

- Code of Federal Regulations Title 21 Parts 210 and 211 – Good Manufacturing Practices
- ICH Guidelines (ICH Q 10, ICH Q 7A, ICH Q 9)
- Guide to Process Validation
- United States Pharmacopeia (USP)
- National Formulary
- ISPE Base Guidelines
- PDA Documents

11.0 Terms and Definitions

The following commonly used terms are identified and defined:

Acceptance Criteria - A set of measurable qualities or specifications used to check out system or equipment installation, operation or performance. Conformance with these qualities or specifications provides a high degree of confidence that a system is installed, operates or performs as intended.

Accuracy – expresses the closeness of agreement between the value that is accepted either as a conventional true value or an accepted reference value and the value found.

Air Lock - Two airtight doors with space in between them.

Alarm - Device or function that signals the existence of an abnormal condition by means of an audible, visual change or both.

ANSI - American National Standards Institute

Approval (Approved) - A document has been approved after it has been reviewed and signed by a group of individuals representing the QA/QC, manufacturing, and engineering disciplines. Other disciplines may partake in the reviews as required.

API – Active Pharmaceutical Ingredient

Audit or Quality Audit - A documented activity performed on a periodic basis in accordance with written procedures to verify, by examination and evaluation of the objective evidence, compliance with those elements of the quality program under review.

Calibration - Comparison of a measurement standard or instrument of known accuracy with another standard or instrument to detect, correlate, report and/or eliminate any variation in the accuracy of the item being compared.

CDER - Center for Drug Evaluation and Research.

Certification - Documented testimony by qualified personnel that a system qualification, validation or revalidation has been performed appropriately and that the results are acceptable.

CFR - Code of Federal Regulations.

cGMP (GMP) - Current Good Manufacturing Practice.

Change Control - A formalized program by which qualified representatives review proposed and actual changes to products, processes, equipment or software to determine their potential impact on the validation status. It provides an audit trail of changes made.

Characteristic - A physical, chemical, functional identifiable property of the product, component or raw material.

Clean-In-Place (CIP) - A system of pumps, tanks and distribution piping designed to circulate detergents, disinfectants and flushing liquids through process equipment systems without disassembling, hand-cleaning and reassembling the system. CIP systems can be semi-automatically or fully automatically controlled.

Compendia Test Methods - Test methods which appear in official compendia such as the United States Pharmacopoeia (USP).

Component - Any material, substance, part or assembly used during product manufacture that is intended to be included in the finished product.

Concurrent Validation –The validation process whereby the equipment or process is tested and qualified during actual production or regular use.

Controls Testing - Testing that verifies switches, controls and soft keys located on the control panel or associated with FCS operate as designed and in conjunction with equipment and operating parameters.

Control Parameter - Those operating variables that are utilized to specify conditions under which the product is to be manufactured.

Critical Instrumentation - Any instrument that provides a record of the process that is used in determining quality of the product.

Critical System - A system whose performance has a direct and measurable impact on the quality of the product. A system determined to be a critical system must be designated as such and operated and maintained per approved procedures.

Design Review - A planned, scheduled, and documented audit of pertinent design aspects that can affect performance, safety or effectiveness.

Detection Limit - The lowest amount of analyte in a sample that can be detected but not necessarily quantitated as an exact value.

DOP (Dioctyl phthalate) - A material that when dispersed as an aerosol is used to leak test high efficiency particulate air filters (HEPA). Alternative methodologies to DOP (due to exposure concerns) are mineral and corn oils.

Environment - The condition, circumstances, influences, and stresses, surrounding and affecting the product during storage, handling, transportation, installation and use.

FAT - Factory Acceptance Testing

FDA - Food and Drug Administration

Functional Testing - Testing that includes manual and automatic testing verifying components within the system (valves, etc.) and the system as a whole operates as designed and in conjunction with equipment and operating parameters.

FRS - Functional Requirements Specifications

Hardware - The physical components of an electronic control system (as contrasted with the software components). These components provide the physical connections to the system (s) or equipment to be controlled. Hardware components include (but are not limited to) the CPU (central processing unit - microprocessor), I/O (input/output - sensors, printers) and relays.

HEPA Filters - High Efficiency Particulate Air Filters.

HPLC – Hi performance liquid chromatography, or, Hi pressure liquid chromatography

HVAC - Heating, ventilation and air conditioning

ICH – International Council on Harmonization

Installation Qualification (IQ) - Documented verification that key aspects of the installation adhere to appropriate codes, approved design specifications and manufacturer's recommendations (where appropriate).

Interlock - Arrangement of signals which perform a logical and sequential function.

LAL – LimulousAmobysite Assay. The test used to determine endotoxin levels in a sample.

Laboratory Qualification - The process by which the staff, instrumentation, and all relevant support systems in a laboratory are demonstrated to be capable of carrying-out a test method and consistently generate correct results in accordance with predetermined acceptance criteria.

Ladder Logic - A diagrammatically representation of the specific functions of an electronic control system.

Linearity - is the assay's ability (within a given range) to obtain test results that are directly proportional to the concentration (amount) of analyte in the sample.

Method Development – The process by which new methods are developed and evaluated for suitability of use as test methods.

Method Transfer – The process by which methods are transferred from the transferring laboratory to receiving laboratories such that performance characteristics are retained within defined acceptance criteria. The transfer process should include qualification of the laboratory to use the method.

Method Validation – The process by which attributes such as accuracy, precision, selectivity, ruggedness and reproducibility of developed methods are formally established against predefined acceptance criteria and documented. Except for stability indication, compendia methods may only require abbreviated method validation studies (e.g., accuracy, linearity, bias, etc.).

NIST - National Institute of Standards and Technology

"Non-critical" Instrumentation - Instrumentation used primarily for convenience, operator ease or maintenance.

Operating Parameter or Variable - Those process variables which are measured to monitor the state of the process.

Operational Qualification (OQ) - Documented verification that systems or subsystems, capable of being changed, perform as intended throughout anticipated operating ranges.

OSHA - Occupational Safety and Health Administration

P&ID –Piping and Instrumentation Drawing - Schematic representation of the installed piping and instruments

Performance Qualification (PQ) - Documented verification that equipment, systems or processes perform as intended throughout specified operating ranges.

pH - Logarithmic measurement of the acidity or alkalinity of a solution.

Precision - expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from sampling of the same homogenous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision, and reproducibility.

Protocol - Written testing plan that includes the objectives and methods for the conduct of a study

Process Validation – Obtaining documented evidence that the process or production of the pharmaceutical product meets the pre-approved acceptance criteria for that product.

Prospective Validation (Validation) - A defined strategy of test procedures which in combination with routine production methods and quality control techniques provides documented assurance that a system is performing as intended and/or that a product conforms to its pre-determined specifications

Preventative Maintenance – The program or procedures used to keep all process systems fully operating within accepted predefined specifications.

Proven Acceptable Range (PAR) - Those values of a control or operating parameter that f between the proven upper and lower operating conditions. The PAR values are derived from developmental validation studies whose intent is, primarily, to establish the operational ranges to be used in the production environment.

Software - The portion of an electronic control system comprised of instructions written in one or more artificial language(s). Some are readable as standard English and others, binary for example, that are only readable by machine or those extremely well versed in the 'machine language'. These instructions provide the specific directions to the electronic control system to perform various functions. Software is frequently user (or self) alterable. This alterability of software results in greater flexibility of the system and greater risk. This risk is offset by instigating software change control measures, security access and using compiled code.

Source Code – The code used by computers or controllers of process systems or equipment. This code is readable only by the machine components themselves (frequently this code is binary) and can be very specific to the

particular machine components in question. Most humans cannot write software directly in machine-readable (compiled) code, therefore, humans typically write code in a higher order language such as Cobol, Fortran, etc. This human readable code is called the source code (because it is the source of the machine-readable code). This source code is compiled (translated) by a computer system from the human readable form to the machine-readable form.

Startup/Commissioning (S/C) –The program or procedure used to perform preliminary testing on equipment or utilities. It provides documentation that the equipment is connected according to design specifications; and that the basic operation is achievable.

Standard Operating Procedure (SOP) – Written instructions that enable a trained person to operate or otherwise perform a given function.

Qualification - The procedure by which equipment, processes and instrumentation are proven to be designed properly and perform adequately and reproducibility as designed.

Quality - The composite of the characteristics, including performance, of an item or product.

Quality Assurance (QA) Program Requirements - As defined in the GMP, the requirements consist of procedures adequate to assure the quality of the manufacturing process and adequate to assure that the following functions are performed: 1) review of production records; 2) approval or rejection of components, drug product containers, closures, in-process materials, packaging materials, labeling, and drug products: approval or rejection of drug products manufactured, processed, packaged, or held under contract by another company; 3) availability of adequate laboratory facilities for testing and, based on test results, determining disposition of components, drug product containers, closures, packaging materials, in-process materials, and drug products; and 4) approval or rejection of procedures and specifications impacting on the strength, quality and purity of the drug product.

Quality Control (QC) Unit - A regulatory process whereby the quality of raw materials and produced product is controlled by inspection and tested for the purpose of preventing production of defective product. This unit is comprised of QA and QC.

Qualification of Methods – The process by which methods are determined to be suitable for analysis of a given test article by a given laboratory.

Quantitation limit - is the lowest amount of analyte in a sample that can be quantitatively determined with suitable precision and accuracy.

Quarantine - Any area that is marked, designated or set aside for the holding of incoming components prior to acceptance examination and finished products until released.

Range - is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity

Reference Instrumentation - Any instrument excluded from the calibration program because of its inability to be calibrated or its infrequency of use.

Regulatory Test Method - A test method that has been approved by a governmental regulatory agency such as the FDA.

Repeatability - expresses the precision under the same operating conditions over a short interval of time. Repeatability is also referred to as "intra-assay precision."

Reproducibility - expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Retrospective Validation – Performing analysis on previous batch records for a given operation. A sufficient number of batches or production runs must be used in the analysis in order to demonstrate reproducibility and compliance with CGMP regulations overall.

Rework – A set of procedures that define the conditions under which a process or batch of product can be mixed into or otherwise redone so as to make it conform to the required specifications for that product.

Robustness – is a measure of the assay's capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage

R&D – Research and Development

Revalidation - The repetition of the validation process or a specific portion of it, to assure that a system is suitable for use after modification or repair. Revalidation is required on a periodic basis to ensure that the process or system continues to operate as intended.

Sanitization - Reduction in the number of microorganisms to a safe or relatively safe level as determined by applicable regulations or the purpose of application.

Sanitizer - Any chemical that kills microbial contamination in the form of vegetative cells.

Specificity – is the ability to assess unequivocally the analyte in the presence of components that may be expected to be present. Typically, these might include impurities, degradants, matrices, etc.

State of Control - A condition in which operating and control parameters of processes or systems are stable and within ranges documented to establish consistent and reliable control of the processes.

System - A number of integrated steps, functions and items of equipment that must be considered as a unit in order to assure supply of a consistent, uniform and high quality component for the manufacture of a product.

System Suitability – Specific tests designed to determine the suitability of the overall test system (including instrumentation, sample preparation and analyst) is suitable for the intended use of the test method. Typical tests utilized for system suitability measure test system precision, specificity and detection.

Transfer Area - Any area of the manufacturing facility, other than the weighing, mixing, or filling areas, where the components, in-process materials, and drug products, and drug product contact surfaces of equipment, containers, and closures after final rinse of such surfaces, are exposed to the plant environment.

Testing – Qualified activities performed by the testing laboratory, utilizing approved, validated, qualified and (if appropriate) successfully transferred methods. These activities accomplish the purpose of establishing testing procedures to ensure accurate determination of the identity, strength, quality and purity of the component/product tested.

Testing Laboratory - The laboratory that performs routine testing for official disposition (e.g., release, stability) of components and/or products. The testing laboratory may be a QA laboratory at a manufacturing site or a contract laboratory whose use is approved in accord with corporate policies/procedures.

Test Method – An approved detailed procedure describing how to test a sample for a specified attribute (e.g., assay), the amount required, instrumentation, reagents, sample preparation steps, data generation steps and calculations used for evaluation.

Test Results – The final calculated results obtained after testing has been completed

USP - United States Pharmacopoeia

Validation Change Control - A formalized program by which qualified representatives review proposed and actual changes to products, processes, equipment and/or software to determine their potential impact on the validation status. Based on impact determinations action is taken that ensures the system retains its validated state.

Validation Protocol - An approved document stating how validation is conducted. The document includes test parameters, product characteristics, required equipment and procedures and acceptance criteria.

Validation Final Report - An approved document of the results derived from executing a validation protocol. The report includes a brief summary of conclusions based on test results of the validation status. Proven acceptable ranges for critical process parameters are designated as determined by the results of the validation study.

Verify - Comparison of a measurement standard of known accuracy with another standard or instrument to detect, correlate or report, but not eliminate, any variation in the accuracy of the item being compared. Verification implies that no adjustment of the compared item is possible to re-establish accuracy.

"Worst Case" - A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

12.0 Change History

4/24/17 - KLB

- Minor typographical error corrections
- Formatting update
- Updated process validation timeline to include new equipment