Standard Operating Procedure

Title: Procedure for Performing Steam in Place (SIP) Validation

Department	Validation/Technical Services		Document no	VAL-225	
Prepared by:		Date:		Supersedes:	
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1. PURPOSE

The objective of this Standard Operating Procedure is to outline the validation approach for sterilisation-in-place (SIP) process validation of all biological production area vessels, both in empty and full states, associated pipework, transfer lines, filters and manifolds at a GMP site.

2. SCOPE

This SOP details the procedure to be carried out when performing validation studies on the vessels, associated pipe work, transfer lines, filters and manifolds for the biological production area at a GMP site.

Validation will be carried out in accordance with an approved protocol or approved protocol plan test sheets. The protocol will provide detailed test procedures, assign responsibilities and define acceptance criteria.

3. RESPONSIBILITY

It is the responsibility of all validation personnel to ensure that validation activities are carried out in accordance with this SOP. Contractors carrying out validation activities on behalf of the Principal (Customer) must comply with the requirements of this document.

General responsibilities for validation activities are defined in VAL-080 Validation Master Plan.

4. SAFETY AND PROCESS SPECIFIC INFORMATION

All safety requirements for relevant areas at a GMP site must be followed at all times.

PPE required:

Safety Glasses, insulated gloves, production coveralls, hearing protection when pumps are operating in the area.

- The appropriate Personal Protective Equipment (PPE) must be used when dealing with the vessels extremes of temperature.
- Wear safety glasses and disposable sterile gloves when performing studies with Biological Indicators (BIs). Ensure all BIs are returned to the QC Microbiology Laboratory for testing or appropriate disposal.
- Ensure that a work permit form “Permit to Work: Approval” form has been completed to authorise validation work on the target equipment(s). Note that to isolate utilities, an additional form “Equipment Isolation Lock-Out and Tag-Out” (Appendix A) must be completed as part of the “permit to Work: Approval” form.
- All access to vessels must be conducted following Form “Equipment Tag Out for Validation” (Appendix B)

5. GLOSSARY/DEFINITIONS

- BI - A biological indicator is a spore strip/ ampoule or inoculated item with a population of spores of no less than 10^6 (for strips and dry BIs) and 10^6 (for Wet BIs) *Geobacillus stearothermophilus* with known D (minimum of 1.5 minutes) and Z values.
- Control BI - A BI of the same lot as those used for testing, but one that was not exposed to the sterilisation cycle which has not been treated in the same manner.

122156	Risk Assessment for the SIP of all Antigen Tanks
102038	Blending Area Transfer Line SIP Risk Assessment
102093	Risk Assessment - Sterilisation of Filling Lines

8. VALIDATION RATIONALE

8.1 Validation Rationale

Sterilization In Place Performance Qualifications and Re-qualification are required in the following circumstances:

- New Equipment, including Vessels, associated pipe work, transfer lines, filters or manifolds
- Changes to the SIP procedure or parameters
- Major changes to vessels, associated pipe work, transfer lines, filters and manifolds as directed by a change control
- Scheduled compliance

8.2 Revalidation Approach

Vessels, transfer lines, filter systems or manifolds used in the biological production area must be re-validated as per the re-validation schedule. For the purposes of re-validation all the vessels are classified as groups based on the volume, internal diameter and the number of connections on the vessels. Only one vessel from each group is to be revalidated. An example of "Schedules and vessel groupings are detailed in Appendix C.

Vessels subject to Department of Agriculture bio-security quarantine rules must be re-validated on an annual basis.

Before the commencement of re-validation activities a review of all previous validations completed on the chosen vessel, transfer line, filter system, intermediate process equipment or manifold shall be conducted.

9. PROTOCOL PREPARATION

9.1 PQ Protocol Preparation

- Protocols for all SIP validation depending on the equipment type are to be raised by completing Appendix D "Sterilisation- In- Place: Validation Protocol Plan Approval" alongside the following documents for the respective SIP execution type:

Equipment Type	Document Number	Document Title
Vessels	Appendix E	Sterilisation In Place – Empty/Full Vessel Protocol
	Appendix F	Sterilisation In Place Validation – Vessel Diagram
	Appendix G	**For new equipment or cycles** Sterilisation In Place – Data Collection Table
Transfer Lines	Appendix H	Sterilisation In Place – Transfer Lines Execution
	Appendix I	Sterilisation In Place Validation – Transfer Line Diagram
	Appendix J	**For new equipment or cycles** Sterilisation In Place Validation – Transfer Lines Data Collection Table

I). The placement of BIs must be completed in accordance with VAL-200 Selection and Use of Biological Indicators during Validation Studies.

- A pressure transducer should also be placed at a suitable location for the continuous monitoring of pressure. Area steam supply pressure readings from DAS software display (iFix) should be recorded manually for the start, middle and end of the run.

10. EXECUTION OF THE PQ PROTOCOL

10.1 A half cycle for any empty vessel and a full cycle for any filled vessel is employed, unless otherwise stated. Review the vessel operation SOP to determine the current validated sterilisation time period(s).

10.2 Synchronise the times of the Graphtec or Eurotherm Data loggers with the DAS time.

10.3 The graphic recorder shall be set to record data in 5 second intervals.

10.4 Place the thermocouples and biological indicators according to the locations selected on form Appendix F or Appendix I diagram.

10.5 Ensure that the vessel and fittings are closed and that all of the bolts have been tightened due to the placement of the thermocouples.

10.6 Ask an area operator to inspect the integrity of system access points.

10.7 If a full vessel trial is required fill the vessel with the required amount of chosen solution in accordance with the relevant procedure stated in the SOP.

10.8 Unless specific training has been completed for operation of the vessel or equipment for the validation personnel engaging in the study, qualified area personnel must conduct vessel or equipment operation during the SIP evaluation process.

10.9 Initiate the sterilisation of the vessel, transfer lines, or manifold according to SOP. During the empty vessel run the inlet filter is sterilised prior to the sterilisation of the tank and associated pipe work.

10.10 However during the validation of the full vessel, only the tank and associated pipe work are required to be sterilised, as the inlet filter sterilisation process was completed during the empty vessel runs.

10.11 If the validation is for a new piece of equipment or process then also document external monitoring point temperatures, pressure inside the vessel or lines and input of (LP) steam every 5 minutes of the run using the form Appendix G or Appendix J Data Collection Table.

10.12 Once the sterilisation process has been completed, cool the vessel and/or transfer lines down in accordance with the relevant procedure stated in the SOP

10.13 After a successful run, retrieve the BIs and send them to the microbiological laboratory for testing. Fill out the relevant form for the relevant type of Biological indicator. (Appendix N EZ Test Crushable Ampoules, and/or Appendix M MagnaAMP Glass Ampoules/SterilAmp II Glass Ampoules, and/or Appendix L MesaStrip Spore Strips)

10.14 Retrieve the data from the graphic recorder and compare the result to the acceptance criteria. Attach a copy of summarised data to the final validation report Appendix K.

APPENDIX B: EQUIPMENT TAG OUT FOR VALIDATION

1. PURPOSE

The purpose of this operating Instruction is to outline the procedure for removing a piece of equipment from routine service for the purposes of conducting validation (also referred to as "tag-out").

2. SCOPE

These procedures apply to all equipment and facilities located at a GMP site.

3. PROCEDURE FOR PLACING EQUIPMENT "TAG-OUT"

3.1. Obtain permission from the equipment owner to place the equipment (or equipment train) out of routine service for validation.

3.2. Complete a label containing the information required as shown in the attached templates (see section 5). The person who places the label must record the date the equipment is "tagged-out", sign and record their contact extension. (N.B. Electronic copies of the labels may be generated from the label templates).

3.3. The label must be securely attached to the equipment in a position such that the label is readily visible. If necessary an additional labels may be placed at critical locations e.g. next to the equipment operation controls.

4. PROCEDURE FOR RETURNING EQUIPMENT TO PRODUCTION USE

4.1 Complete the label field "Returned By" and sign and date the label.

- Complete equipment usage/log book
- Attach the label (or a copy) to equipment usage/manufacturing records
- Attach the label (or a copy) to validation report

5. EQUIPMENT "TAG-OUT" LABEL TEMPLATES

5.1 Large Format Label Template

[Company Name] *[Address]*

UNDERGOING VALIDATION

DO NOT USE WITHOUT VALIDATION APPROVAL

Appendix C: Rationale and Schedule for Steam in Place (SIP) Validations on Tanks, Transfer Lines, Filters and Manifolds - Example

This document lists all of the Tanks, Transfer Lines, Filters and Manifolds that require validation and the schedule of each validation. This document must be reviewed yearly in January

1.0 Table of equipment, associated risk assessments and validation schedule

Area	Equipment	Equipment Number	Risk Assessment Project Number	SIP Validation Status	Project Number	Date Completed	Scheduled Date
Filling	Tank	FT01		Validated			
		FT02		Validated			
		FT03		Validated			
		FT04		Validated			
		FT05		Validated			
		FT06		Validated			
Blending	Tank	BT01		Validated			
		BT02		Validated			
		BT04		Validated			
		BT05		Validated			
		BT06		Validated			
		BT07		Validated			
		BT08		Validated			
Antigen	Tank	IT01		Validated			
		IT02		Validated			
		IT03		Validated			
		IT04		Validated			
		IT08		Validated			
		IT09		Validated			
		PT01		Validated			
		PT02		To be validated			
		MV01		Validated			
		MV03		Validated			
		CV04		Validated			
		CV05		Validated			
		CV06		Validated			
		FV02		Validated			
		MV04		Validated			
Antigen and Blending	Filters	Blending and Antigen Filters		Validated			
Filling	Transfer Lines	Filling Lines FM01 and FM02		Validated			

1.4 Revalidation of tanks in the Antigen Area

All tanks on site must be validated initially. Regarding the initial validation the number of runs required, detailed process and acceptance criteria is outlined in this procedure.

For the purpose of revalidation not all tanks in the Antigen Area will be validated each year. Only the three (3) culture vessels (CV04, CV05 and CV06) must be re-validated each year because are used to sterilize Bio Security material. Thus, any equipment used to sterilise AQIS material must be validated on an annual basis. The remaining tanks have been categorized into the following nine groups shown in the table below and one tank from each group will be revalidated every two years. The tanks have been categorized according to tank volume, internal diameter and the number of connections to the tank.

Table 8

Tank Group	Tank Number	Maximum Volume	Internal Diameter	Number of connections
1a	IT01	4000L	152cm	15
	IT02			
2a	IT03	6000L	180cm	15
	PT02			
3a	IT04	6000L	180cm	19
	IT08			
4a	IT09	10000L	230cm	14
5a	PT01	4000L	125cm	15
6a	MV01	500L	60cm	9
7a	MV03	500L	70cm	8
8a	FV02	750L	55cm	16
9a	MV04	350L	80cm	7

Revalidation of tanks will only require one successful run to be completed for each state empty and full, except for MV01, MV03 and MV04 tanks where one run is required to be completed when the tank is in an empty state only.

In regard to full tank sterilizations, water has been chosen as the solution to be sterilized and the stirrer should be set to the normal production mixing speed must be used.

Appendix E: Sterilisation in Place – Vessel Execution Record

Project No	Vessel No	Run No	Number of Runs

1. OBJECTIVE

Using an appropriate sterilisation cycle, demonstrate that the tested cycle will, with a high degree of assurance sterilise the vessel. Each cycle should consider the location(s) within a vessel considered to demonstrate worst case conditions.

2. PROCEDURE

2.1. Standard Procedures and Operator Instructions

Before commencement of the qualification, ensure a pre-sterilisation documentation review has been conducted as per VAL-270 “Critical Documentation Verification during a Validation Study” and documented.

Initial / Date

NOTE: THIS DOCUMENT MUST BE REPRODUCED FOR EACH CYCLE

Load Description (include material type and volume if full vessel cycle)

2.2. Test Instrumentation

Instrument Number	Instrument Name or Description	Date of Calibration	Calibration Due Date

2.3 Calibration and Verification of Test Devices

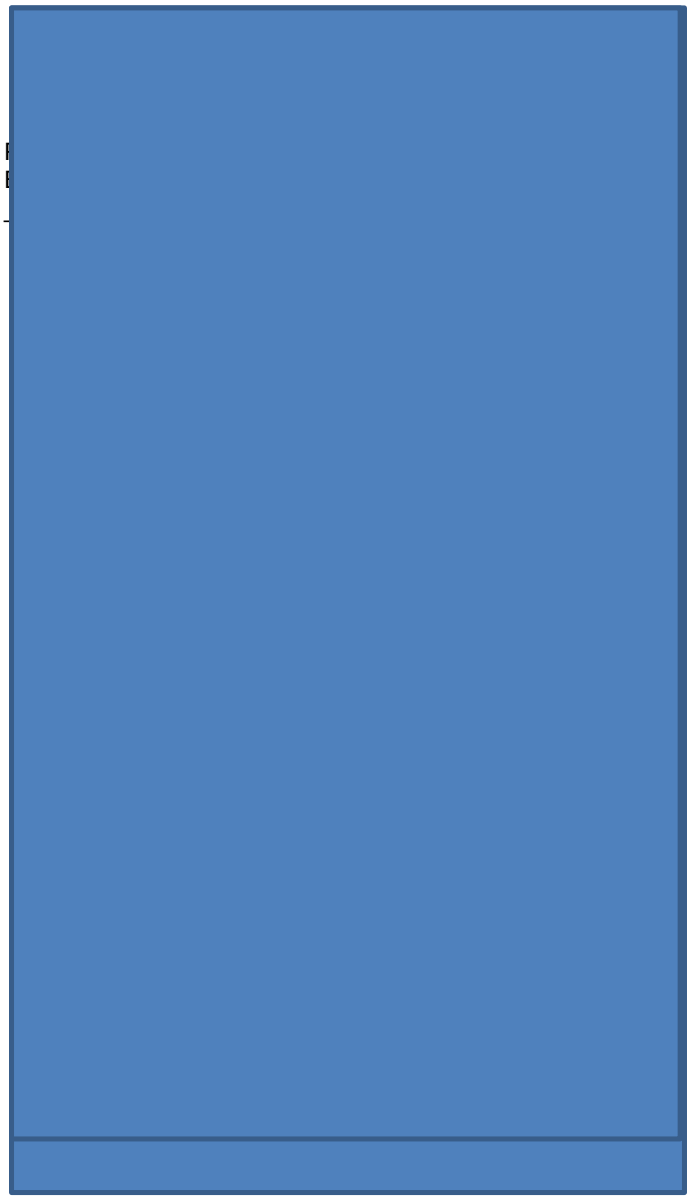
Confirm the data logger has a minimum sample rate of 5 seconds and all test equipment has been calibrated and or verified as per written instructions.

Initial / Date

Appendix F: Sterilisation in Place Validation – Vessel Diagram

Project No		Vessel No		Run Number	

Location	BI	T/C	Ext. Temp
Air Inlet Filter			
Air Exhaust Filter			
CIP Sprayball / Inlet			
Pressure Gauge			
Inoculation Port			
Vessel Pressure Relief Valve			
Manway			
Sight glass			
Stirrer Well			
Base Valve			
Sample Valve			



Draw on Stirrer, CIP sprayball configuration and additional input lines where applicable.

Recorded By:_____ Date: _____

2.4. Biological Indicators (BIs)

Sign/Date

Verify that the BIs have not expired and record the population, organism, lot number, manufacturer and expiration date of each lot.

Indicator Type (cross out non relevant indicators)	EZ-Test Crushable Ampoule (DRY)	Spore Strip (DRY)
Lot Number		
Organisms	*G.Stearothermophilus*	*G.Stearothermophilus*
Population		
Manufacturer	Mesalabs	Mesalabs
Manufacture Date		
Expiration Date		

2.5. Thermocouples and Biological Indicator placement

Sign/Date

Distribute the calibrated thermocouples and biological indicators at the depicted locations in Appendix I.

2.6. Conduct Sterilisation of the Transfer Line(s)

2.6.1. Start the data logger with a minimum data sample rate of 5 seconds and perform the cycle to be validated.

Sign/Date

2.6.2. **Temperature Stabilisation:** Record the time it takes for the internal temperature to stabilise at the required value (≥ 121.0°C).

Start Time	Finish Time	Total Stabilisation Time (min)	Stabilised Temperature (°C)

Appendix J: Sterilisation in Place Validation – Transfer Lines

Project Number	Transfer Line	Run Number	No. Runs
	Source:		
	Terminus:		

Transfer Line External Point SIP Manual Data Collection Record from Source Point to Line Terminus

Time										
Monitoring Point Location	Temp (°C)	Temp (°C)	Temp (°C)	Temp (°C)	Temp (°C)	Temp (°C)	Temp (°C)	Temp (°C)	Temp (°C)	Temp (°C)
Pressure	kPa	kPa	kPa	kPa	kPa	kPa	kPa	kPa	kPa	
Input Steam										
Gauge in Place										

Performed by: _____ **Date:** _____ **Checked by:** _____ **Date**: _____

Validation Reporting				
Instructions / Attachment / Reporting Requirement		**Reporting Requirement (Pass/Fail/ Completed/Attached)**	**Deviation(s) (Yes - #(s) / No)**	**(Sign/Date)**
1	Validation Protocol Plan "Form-875 Sterilisation In Place Validation Protocol Plan Approval" was completed as approved.			
2	Thermocouple temperature calibration verification sheets are attached and have met the pre and post-use acceptance criteria for the respective logger.			
3	Following forms are completed and attached for all Vessel SIP trials • Form-880 Sterilisation In Place Vessel Execution Record (**Appendix E**) • Form-885 Sterilisation In Place Validation Vessel Diagram (**Appendix F**) • Form-890 Sterilisation In Place Validation - Data Collection Table (**Appendix G**) Following forms are completed and attached for all Line SIP trials. • Form-895 Sterilisation In Place Validation – Transfer Lines (**Appendix J**) • Form-900 Sterilisation In Place Validation – Transfer Line Diagram (**Appendix I**) • Form-905 Sterilisation In Place – Transfer Lines Execution (**Appendix H**)			
4	• Form-910 Critical Documentation Verification – Post Execution, and • Form-915 Critical Documentation Verification – Pre-Execution, are completed.			
5	SIP Trial Data Sheets are completed for each trial			
6	SIP Trials have met their respective acceptance criteria			
7	Department of Agriculture requirements satisfied (if applicable)			
8	"Trial execution summary" table completed			
9	"Attachments List" table completed			

Deviation Reports List			
Deviation Number	**Brief Description of the Deviation Report**	**Critical Impact on Validation Trial Status (Yes / No)**	**(Sign/Date)**
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			

Appendix M: Biological Indicator Test Results Sheet – Glass Ampoules

Procedure

Fill out table and transfer sheet to Quality Control with all samples.

Cycle Number:		Run #:		Initials/Date:	
QC Serial Number:					
Commenced Incubation at	^{o}C	Time:		Initials/Date:	

1. Place the ampoules in the incubator rack and incubate immediately for 48h at (60 ± 2)^{o}C.
2. Record the examining time and results in the table below.

Acceptance Criteria - Geobacillus stearothermophilus

- **Vibrant Yellow colour** indicates bacterial growth.
- **Clear Purple, Violet, Brown or Bourbon colour** indicates adequate sterilisation.

Vibrant Yellow

Purple

Violet

Brown or Bourbon Colour

Table 1. Test Results for Indicators				
Position	**Op. Init.**	**Date**	**Biological Indicator Result** **Purple, Violet, Brown or Bourbon = –** **Vibrant Yellow = +**	**Sign/Date**
Control				
Test Result: ☐ **Pass** ☐ **Fail**				
Comment:				
Tested by/Date		**Verified by/Date**		
Review by/Date				

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Appendix P: Calibration Verification Record

Project ID: _____

Datalogger ID: _____ Permitted error: _____

Calibrator detail: _____ Record Date / Time _____

Calibration Range | Lower calibration temp. set point (ºC): _____ | Upper calibration temp. set point (ºC): _____

Pre-use Verification: ❑ Post-use Verification: ❑

Thermocouple Channel/Number	Acceptance Criteria	Temperature Verification Set Point (ºC)	Actual Temperature (ºC)	Pass/ Fail

Operator initial: _____ Date: _____

Comments / _____

Deviation #: _____