Frederick National Laboratory for Cancer Research, Frederick, **MD**

BDP

Biopharmaceutical Development Program

Standard Operating Procedure

Title: Preparation of Vials, Stoppers, and Crimps for CGMP Filling of Final Product

SOP Number: 15105

Revision Number: 09

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[redacted]

Originator/Date:

Approval/Date:

Approval/Date:

Table of Contents

1.0 Purpose

To describe the procedures for requesting, preparation, and sterilization of vials, stoppers, and crimps used in filling of final product.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted]

2.0 Scope

The proceduresin this SOP govern the requesting and preparation of container and closure components used in the filling of Current Good Manufacturing Practices (cGMP) reduct by Biopharmaceutical DevelopmentProgram (BOP) manufacturing personnelin the-. This procedureapplies both to manual and automated filling systems. Preparaiton of Biopharmaceuitcal Quality Assurance (BQA) released container and closure components will occur in-- . The BOP uses Westar processed stoppers (pre-washed by West Pharma ces) as the main closure for glass vials. For components prepared in -- sterilization will normally occur via a ass-throughdry heat oven (OVEN-003-A) or autoclave AUTO-005-A) int . Sterilized components may be unloaded into if filling is to be pe orme at a location other than the sterile core suite of rooms. pon un oading the components from the sterilizer place them into a tertiary container that will maintain their cleanliness during tran- ort. When using AUT0-011-A for sterilization, trans- rt the material to be autoclavedto . Unload sterilized components into and place them into a te lary con amer that will maintain their cleanliness during ranspo .

Biopharmaceutical Quality Engineering (BQE) releaseof the utilized areas will be required for the facilities prior to work beginning. Critical information related to this process will be recorded on attachments included in this SOP.

3.0 Authority and Responsibility

3.1 The Manager, Manufacturing, BOP, has the authority to define this procedure.

3.2 The Manager, Manufacturing, BOP, is responsible for ensuring that BOP manufacturing personnel are trained in this procedure and documentationof training with BQA.

3.3 BOP manufactu ring personnel are responsible for performing the work as specified in this SOP.

3.4 BQA is responsible for quality oversight of this operation.

4.0 Preparation of Rooms

4.1 Clean the [redacted] as per **SOP *19408 - Cleaning and Disinfection of CGMP Areas in the [redacted].***

4.2 Stage all required components (vials, stoppers, crimps, etc.)

4.3 Verify that all items have been BQA released and are within their expiration date.

4.4 Ensure area and utilities are released for GMP processing as per **SOP *21554- GMP Area Status Management.***

5.0 Preparation of Pans

5.1 The parts washer will be **operated** according to **SOP *19411- Operation and Maintenance of the Girton Parts Washer,*** using the CIP 100/200 wash cycle.

5.2 Prior to vials being wa-sh d for a reduction run, vial pans will be washed in the Girton parts washer located in . The washing of the pans will be performed within a month before the vials are o e washed.

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5.3 After the pans and lids are was- ed, the an lids will be secured onto the pans so the pans are not open to the air in . Clean and secur will be labeled with the wash date and placed msl es orage cage located in- or-

[redacted]

6.0 Preparation of Vials

6.1 Obtain and complete **Form 15105-01** (**Attachment 1**), when preparing vials.

6.2 Apply 1 BDP raw material release label from each lot of glass vials used to **Form 15105-01 (Attachment 1).**

6.3 Visually screen vials as they are removed from their packaging. Discard damaged, dirty, or otherwise unacceptable vials and document the number of vials rejected on **Form 1515-01 (Attachment 1**). Notify the Supervisor before proceeding if vials appear generally abnormal.

6.4 Wash vials per ***SOP 15145- Operation and Maintenance of the PennTech Vial Washer.***

6.5 Package glass vials for depyrogenation per the following instructions.

6.5.1 Remove vials from washer and place upright in a clean stainless-steel pan obtained from the pan storage cart.

6.5.2 Vials for closure integrity testing will be placed upright in the clean stainless-steel crimp check pan obtained from the pan storage cart.

6.5.3 Dry the vials in the oven prior to depyrogenation. The lid will be securely placed onto the pan. The pans will be unwrapped at this time.

6.5.3.1 Run the depyrogenation oven on the dry vials cycle per **SOP *15146* - *Operation and Maintenance of the TPS Depyrogenation Oven.*** Note on **Form 15105-1** that the vials were dried.

6.5.3.2 On completion of the drying cycle, remove pans from the oven.

6.5.4 Wrap the pan with heavyweight oil free aluminum foil and seal with heat-resistant tape.

6.5.5 A single wrappin of aluminum is re uired if the an will be removed from oven into [redacted] for use in fill areas . If the pan is removed in [redacted] for use in other fill areas, a ou e wrapping of aluminum foil will be required

6.6 Label the outside of each pan with the following information:

6.6.1 Vial BDP part number

6.6.2 Vial BDP lot number

6.6.3 Shelf life of processed vials (16 weeks from the sterilization date)

6.6.4 Number of vials

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted]

6.6.5 Oven load number and run date

6.6.6 Initials and Date of the individual recording this information

6.7 Vials for calibration, weight checks and will be packaged in groups of 10 vials and double wrapped with heavy duty oil-free aluminum foil. They will be placed on the top shelf of the oven.

6.8 Sterilize by dry heat sterilization using the depyrogenation cycle per ***SOP 15146 - Operation and Maintenance of the TPS Depyrogenation Oven***.

6.9 Review the oven chart at the end of the cycle. Verify that the cycle ran according to oven load validation specifications. Sign and date the chart. A copy of the oven chart is required for cGMP BPR's.

6.10 If the oven did not perform properly, notify the Supervisor before proceeding.

6.11 Unload into [redacted].

6.11.1 Vials may be unloaded into [redacted] if filling is to be performed at a location other than the sterile core suite of rooms. Upon unloading the vials from the sterilizer place them in a tertiary container that will maintain their cleanliness during transport.

6.11.2 Sterilized vials should be stored in [redacted] if not being used immediately.

6.11.2.1 Vials for automated fills can be moved into the curtained area of [redacted] once the project cleaning o [redacted] is completed. Pans of vials moving into [redacted] are sprayed with 70% IPA as they move into this ISO5 area.

6.11.2.2 Vials for manual fills in the sterile core will be moved into [redacted] once the project cleaning of [redacted] is completed

6.12 Complete **Form 15015-01** for vial inspection, washing, and sterilization.

7.0 Preparation of Stoppers

7.1 Obtain and complete **Form 15105-02 (Attachment 2)**, when preparing stoppers.

7.2 Stoppers should be free of dust and dirt upon receipt. If not, notify the Supervisor.

7.3 If necessary to repackage the needed number of stoppers from a larger bulk container, this should be done using sterile gloves and sleeve covers in a BSC. Take care to preserve the cleanliness and integrity of the remaining stoppers in the bulk container.

7.4 Westar stoppers are pre-washed and siliconized by the manufacturer. No further cleaning or treatment is necessary.

7.5 If the stoppers are not pre-cleaned at the manufacturer, wash and siliconize, the stoppers, if required as per ***SOP 15103 - Operation of the DCI Washer*** Package Stoppers.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

7.5.1 Place approximately 1000 stoppers or less into an autoclave pouch, per Section 7.3. It may be necessary to divide the stoppers into more than one pouch depending on the quantity required. Place the stoppers into a second autoclave pouch. Pouches should be oriented in the autoclave to allow for steam penetration.

7.6 Label the outside of each pouch with the following information.

7.6.1 Stopper BDP part number

7.6.2 Stopper BDP lot number

7.6.3 Autoclave MEF #, run number and run date

7.6.4 Shelf life of processed stoppers (16 weeks from the sterilization date)

7.6.5 Approximate number of stoppers

7.6.6 Initials and Date of individual recording this information

7.7 Steam sterilizes the stoppers as per ***SOP 19500 - Operation and Maintenance of the BMT Steam Sterilizers.***

7.8 Autoclaved stoppers may be unloaded into [redacted] if filling is to be performed at a location other than the sterile core suite of rooms. Upon unloading the stoppers from the sterilizer place them in a tertiary container that will maintain their cleanliness during transport. When using AUTO-011-A for sterilization, unloaded stoppers must be placed into a tertiary container that will maintain their cleanliness during transport.

7.9 Review the autoclave printout at the end of the cycle. Verify that the cycle ran according to the autoclave load validation specifications. Sign and date the printout. A copy of the autoclave printout is required for cGMP BPR's.

7.10 If the autoclave did not perform properly, notify the Supervisor before proceeding.

7.11 Unload the stoppers into [redacted] (if autoclave AUTO-011-A is required).

NOTE: Stoppers may be unloaded into [redacted] if filling is to be performed at a location other than the sterile core suite. Upon unloading the stoppers from the sterilizer place them in a tertiary container that will maintain their cleanliness during transport.

7.12 Sterilized stoppers should be stored in [redacted] if not being used immediately. Stoppers for automated fills can be moved into the curtained area of [redacted] or [redacted] once the project cleaning of appropriate room is completed. Pouches of stoppers moving into [redacted] are sprayed with 70% IPA as they move into the ISO5 area.

7.13 For preparation of Lyophilization stoppers only. Place the stoppers in double autoclaved pouches. After autoclaving, dry the stoppers in the depyrogenation oven per ***SOP 15146 - Operation and Maintenance of the TPS Depyrogenation Oven***, using the stopper drying cycle to remove residual moisture from the stoppers. The autoclave bags must be positioned with the Tyvek side down.

7.14 Complete **Form 15015-02** for stopper washing and sterilization.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

8.0 Preparation of Crimps/Seals

8.1 Obtain and complete **Form 15105-03 (Attachment 3)**, when preparing crimps.

8.2 Visually screen the crimps/seals for cleanliness and for physical imperfections (bent crimps are most common). Discard any dirty or bent crimps.

8.3 Siliconize the crimps/seals if they will be used with the Flexicon filler as per ***SOP 15121 - Siliconization of Aluminum Seals***.

8.3.1 To avoid storage of wet/damp aluminum seals, all seals will be dried immediately following siliconization.

8.3.2 If sterilized crimps/seals exceed their autoclave shelf life, they may be re-sterilized an additional time and then used within their new shelf life expiration date. The new expiration date of second sterilization will be added to the outside autoclave pouch with other identification listed in Section 8.5.

NOTE: Crimps/seals for manual fills do not require siliconization. If they exceed their autoclave expiration date they may be re-sterilized one time and used within their new expiration date. The new expiration date of second sterilization will be added to the outside autoclave pouch with other identification listed in Section 8.5.

8.4 Package the Crimp/Seals.

8.4.1 Place the crimps/seals approximately 1000 or less into an autoclave pouch. It may be necessary to divide the crimps/seals into more than one pouch depending on the quantity required.

8.4.2 Place a pouch of crimps/seals into a second pouch to sterilize. Pouches should be oriented as necessary to allow for steam penetration.

8.5 Label the outside of each pouch with the following information.

8.5.1 Crimp/seal BDP part number

8.5.2 Crimp/seal BDP lot number

8.5.3 Approximate number of crimps/seals

8.5.4 If siliconized, indicate Date of Siliconization

8.5.5 Autoclave MEF #, run number and run date

8.5.6 Shelf life of processed crimps/seals (16 weeks from the sterilization date)

8.5.7 Initials and Date of the operator recording this information.

8.6 Steam sterilizes the crimp/seals as per ***SOP 19500 - Operation and Maintenance of the BMT Steam Sterilizers***.

8.7 Autoclaved crimp/seals may be unloaded into [redacted] if filling is to be performed at a location other than the sterile core suite of rooms. Upon unloading the stoppers from the sterilizer place them in a tertiary container that will maintain their cleanliness during

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

transport. When using AUTO-011-A for sterilization, unloaded stoppers must be placed into a tertiary container that will maintain their cleanliness during transport.

8.8 Review the autoclave on screen report and printout at the end of the cycle. Verify that the cycle ran according to specifications and is acceptable. Sign and date the printout. A copy of the autoclave printout is required for cGMP BPR's.

8.9 If the autoclave did not perform properly, notify the Supervisor before proceeding.

8.10 Unload the crimps/seals into [redacted] (if autoclave AUTO-011-A is required).

NOTE: Crimps/seals may be unloaded into [redacted] if filling is to be performed at a location other than the sterile core suite. Upon unloading the crimps/seals from the sterilizer place them in a tertiary container that will maintain their cleanliness during transport.

8.11 Sterilized crimp/seals should be stored in [redacted] if not being used immediately. Crimp/seals for automated fills can be moved into the curtained area of [redacted] or [redacted] once the project cleaning of appropriate room is completed. Pouches of stoppers moving into [redacted] are sprayed with 70% IPA as they move into the ISO5 area.

8.12 Complete **Form 15015-02** for stopper washing and sterilization.

9.0 Shelf-Life of Prepared Vials, Stoppers and Crimps

9.1 The shelf-life of depyrogenated vials is sixteen (16) weeks from the depyrogenation oven run date based on current shelf life studies in PQ-115-E.

9.2 Stoppers or crimps/seals are given a shelf life of sixteen (16) weeks from the date of autoclaving, based on current shelf life studies in PQ-119.

10.0 Documentation

10.1 Completed copies of **Forms 15105-01, 15105-02, and 15105-03** from this SOP are included with the BPR for the finished product.

11.0 References and Related Documents

11.1 **SOP 15103** *Operation of the DCI Washer*

11.2 **SOP 15121** *Siliconization of Aluminum Seals*

11.3 **SOP 15145** *Operation and Maintenance of the PennTech Vial Washer*

11.4 **SOP 15146** *Operation and Maintenance of the TPS Depyrogenation Oven*

11.5 **SOP 19408** *Cleaning and Disinfection of CGMP Areas in the* [redacted]

11.6 **SOP 19411** *Operation and Maintenance of the Girton Parts Washer*

11.7 **SOP 19500** *Operation and Maintenance of the BMT Steam Sterilizers*

11.8 **SOP 21554** *GMP Area Status Management*

11.9 **PQ-115-E** Shelf Life Stability for Wrapped Pans of Depyrogenated Vials

11.10 **PQ-119** Shelf Life Stability for Stoppers and Crimps

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

12.0 Attachments

12.1 Attachment 1 Form 15105-01, Vial Preparation.

12.2 Attachment 2 Form 15105-02, Stopper Preparation.

12.3 Attachment 3 Form 15105-03, Crimp/Seal Preparation.

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 1
Form 15105-01, Vial Preparation

FNLCR, BDP
Form No.: 15105-01
SOP No.: 15105
Revision 09: MAY 31 2019

VIAL PREPARATION

Project Description:	
Project Number	Project Lot Number(s):
Recorded by/Date:	Verified by/date:

VIAL IDENTIFICATION

Description		
BDP Part#	BDP R#	Expiration
BDP Part#	BDP R#	Expiration
Recorded by/date:	Verified by/date:	

Apply 1 BDP Label
from each lot of Vials

VIAL INSPECTION

Number of vials inspected	
Number of vials rejected	
Reject Description: (Damaged □ #____) (Dirty □ #_____) (Other □ # _____)	
Number of vials approved for use	
Performed by/date	Verified by/date

VIAL PAN INSPECTION

(SOP 19411-*Operation and Maintenance of the Girton Parts Washer*)

Vial Pans washed prior to use (Yes / No)	Date of Pan washing:
Pan Inspection and number used: (Clean and free of debris □ #_____) (Rejected □ #_____)	
Performed by/Date:	Verified by/Date:

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 1 (Continued)
Form 15105-01, Vial Preparation

FNLCR, BDP
Form No.: 15105-01
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VIAL WASHING
(SOP 15145-*Operation and Maintenance of the PennTech Vial Washer*)

Wash Cycle Selected (record vial size, neck finish)	
Verify cycle parameter listed match SOP 15145	(YES / NO)
Any Alarms / Faults (if yes, comment below)	(YES / NO)
Alarms corrected / faults corrected	(YES / NO / N/A)
Date(s) vials washed	
Number of vials washed	
Number of vials discarded (unwashed/washed/broken/unused)	
Performed by/date	Verified by/date

Comments: _____

_____

VIAL DRYING and STERILIZATION
(SOP 15146-*Operation and Maintenance of the TPS Depyrogenation Oven*)

Vials Dried in TPS Depyrogenation Oven using Program Cycle 1		(YES / NO)
Oven cycle reviewed and acceptable? (YES / NO)	Vials Dried Date:	
Performed by/Date:	Verified by/Date:	

Vials Sterilized in TPS Depyrogenation Oven using Program Cycle 2			(YES / NO)
Aluminum Foil Part #	Lot #		Expiration:
Total number of vials in pans for sterilization		Total number of Pans	
Total number of vials in Foil sleeves for sterilization (10 vials/sleeve)			
Total number of vials in crimp check pan for sterilization			
TPS Depy.Oven load #	TPS Depy. Oven Started by/ Date:		
Sterilization Expiration Date (16 weeks from autoclave run date):			
Oven cycle reviewed and acceptable?	(YES / NO)		
Performed by/date:	Verified by/date		

Comments: _____

_____

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 2
Form 15105-02, Stopper Preparation

FNLCR, BDP
Form No.: 15105-02
SOP No.: 15105
Revision 09: MAY 31 2019

STOPPER PREPARATION

Project Description:	
Project Number:	Project Lot Number(s):
Recorded by/Date:	Verified by/date:

STOPPER IDENTIFICATION

Description		
BDP Part#	BDP R#	Expiration
BDP Part#	BDP R#	Expiration
Westar treated stoppers do not require washing and siliconization		Westar (YES / NO)
Recorded by/date:	Verified by/date:	

STOPPER WASHING or RINSING
(*SOP-15103 Operation of the DCI Washer*)

DCI Washer MEF		Air POU ID		WFI POU ID	
Volume of WFI used (L)		Duration of Wash/Rinse:			
Performed by/date:		Verified by/date:			

SILICONIZATION
(*SOP-15103 Operation of the DCI Washer*)

DCI Washer MEF		Air POU ID		WFI POU ID	
35% Dimethicone Emulsion	BDP part#	BDP R#		Expiration	
Approximate Volume of 35% Dimethicone Emulsion used (mL)					
Approximate Volume of WFI used (L)					
Number of Stoppers Siliconized					
Performed by/date:		Verified by/date:			

STOPPER STERILIZATION
(*SOP-19500 Operation and Maintenance of the BMT Steam Sterilizers*)

Number of stoppers prepared for sterilization				
Number of stoppers per Autoclave bag				
Autoclave bag	BDP part #	BDP R#		Expiration
Autoclave bag	BDP part #	BDP R#		Expiration
Autoclave MEF#		Autoclave Recipe ID (load #)		
Autoclave Sterilization Run Date:				
Sterilization Expiration Date (16 weeks from autoclave run date):				
Autoclave cycle reviewed and acceptable?		(Yes / No)		
Performed by/date:		Verified by/date:		

This procedure is made available through federal funds from the National Cancer Institute, NIH, under contract [redacted].

Attachment 3
Form 15105-03, Crimp/Seal Preparation

FNLCR, BDP
Form No.: 15105-03
SOP No.: 15105
Revision 09: MAY 31 2019

CRIMP/SEAL PREPARATION

Project Description:	
Project Number:	Project Lot Number(s):
Recorded by/Date:	Verified by/date:

CRIMP/SEAL IDENTIFICATION

Description		
BDP Part#	BDP R#	Expiration
BDP Part#	BDP R#	Expiration
Recorded by/date:	Verified by/date:	

CRIMP/SEAL SILICONIZATION

(SOP- 15103 Operation of the DCI Washer)

Recommended for Flexicon FMB200 Operation – N/A section if not performed

DCI Washer MEF		Air POU ID		WFI POU ID	
35% Dimethicone Emulsion	BDP part#		BDP R#		Expiration
Approximate Volume of 35% Dimethicone Emulsion used (mL)					
Approximate Volume of WFI used (L)					
Number of Crimp/Seals Siliconized					
Performed by/date:		Verified by/date:			

CRIMP/SEAL STERILIZATION

(SOP-19500 Operation and Maintenance of the BMT Steam Sterilizers)

Number of Crimp/Seals prepared for sterilization			
Number of Crimp/Seals per Autoclave bag			
Autoclave bag	BDP part #	BDP R#	Expiration
Autoclave bag	BDP part #	BDP R#	Expiration
Autoclave MEF		Autoclave Recipe ID (load #)	
Autoclave Sterilization Run Date:			
Sterilization Expiration Date (16 weeks from autoclave run date):			
Autoclave cycle reviewed and acceptable?		(Yes / No)	
Performed by/date:		Verified by/date:	

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