

TABLE OF CONTENTS

LIST OF TABLES	1
LIST OF FIGURES	2
3.2.P.3.3. FILL AND FINISH –PRE-FILLED SYRINGE (FROZEN, PLASTIC) [PUURS]	3
3.2.P.3.3.1. Flow Diagram	3
3.2.P.3.3.2. Drug Product Formulation Process Description	5
3.2.P.3.3.2.1. Thawing and Pooling of Tris/Sucrose Drug Product Intermediate	5
3.2.P.3.3.2.2. Dilution of Tris/Sucrose Drug Product Intermediate to 0.1 mg/ml	6
3.2.P.3.3.3. Fill and Finish Process Descriptions	6
3.2.P.3.3.4. Sterile Filtration	6
3.2.P.3.3.5. Preparation of Syringes and Plunger Stoppers	7
3.2.P.3.3.6. Aseptic Filling and Plunger Placement	8
3.2.P.3.3.7. Visual Inspection	9
3.2.P.3.3.8. Assembly, Labeling, Packaging and Frozen Storage	9
3.2.P.3.3.8.1. Storage, Packaging and Shipment of BNT162b2 Drug Product	10
3.2.P.3.3.9. Hold Times	11
3.2.P.3.3.10. Reprocessing	11

LIST OF TABLES

Table 3.2.P.3.3-1. Process Parameters for Thawing of the Tris/Sucrose DPI	6
Table 3.2.P.3.3-2. Process Parameters for Second Concentration Adjustment Step to 0.1 mg/ml	6
Table 3.2.P.3.3-3. Material Attributes and Process Parameters for Sterile Filtration	7
Table 3.2.P.3.3-4. IPT-C Tests for Sterile Filtration	7
Table 3.2.P.3.3-5. Process Parameters for Aseptic Filling	8
Table 3.2.P.3.3-6. IPT-C Test for Aseptic Filling	8
Table 3.2.P.3.3-7. Additional Process Control for Aseptic Filling	8
Table 3.2.P.3.3-8. Process Parameter for Frozen Storage	10

Table 3.2.P.3.3-9. Process Parameters for Product Handling, Redistribution and Storage During Transport	10
Table 3.2.P.3.3-10. Fill and Finish Process Hold Times	11

LIST OF FIGURES

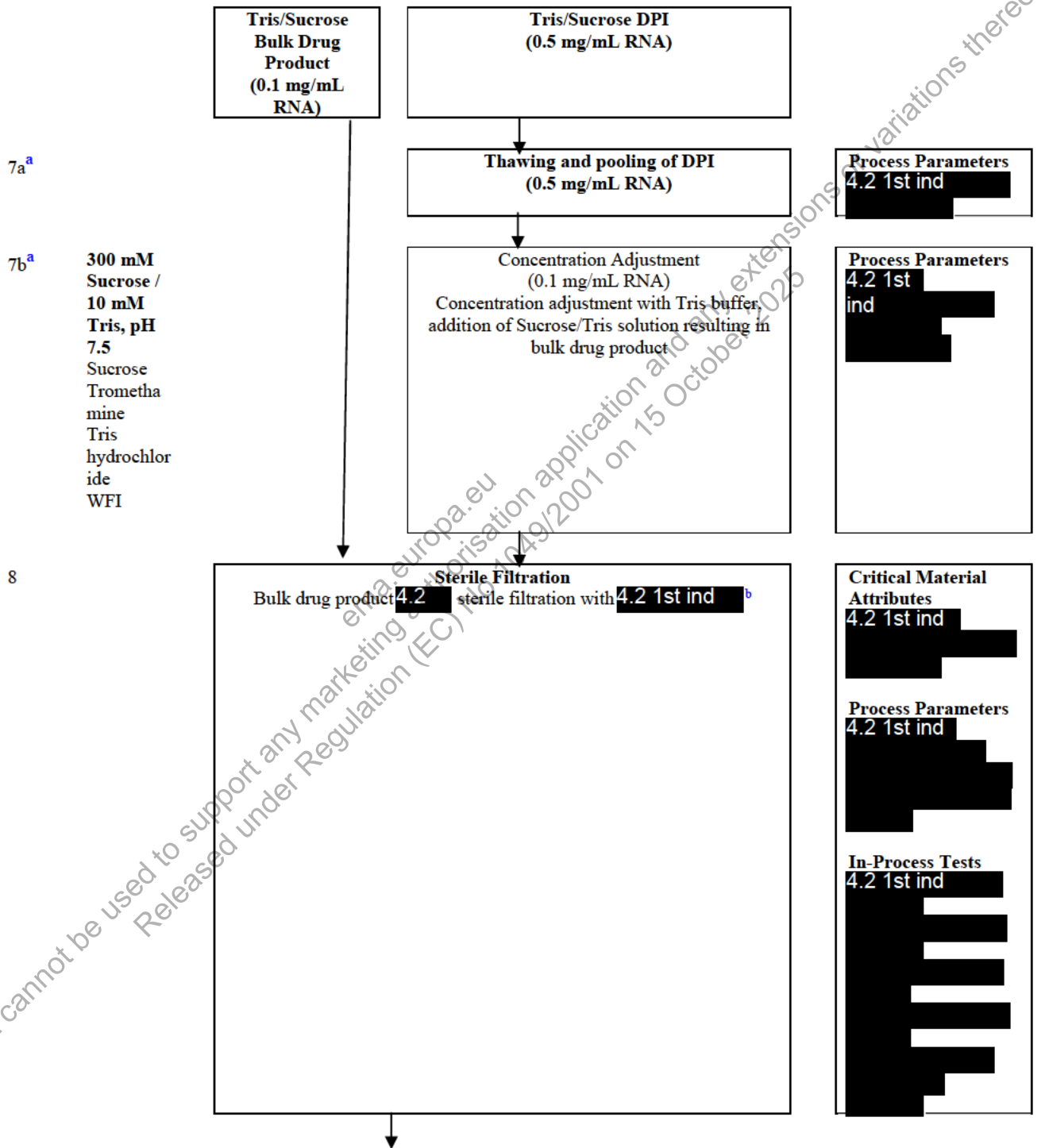
Figure 3.2.P.3.3-1. Flow Diagram of the BNT162b2 Tris/Sucrose Drug Product Fill and Finish Manufacturing Process and Process Controls	4
---	---

3.2.P.3.3. FILL AND FINISH –PRE-FILLED SYRINGE (FROZEN, PLASTIC) [PUURS]

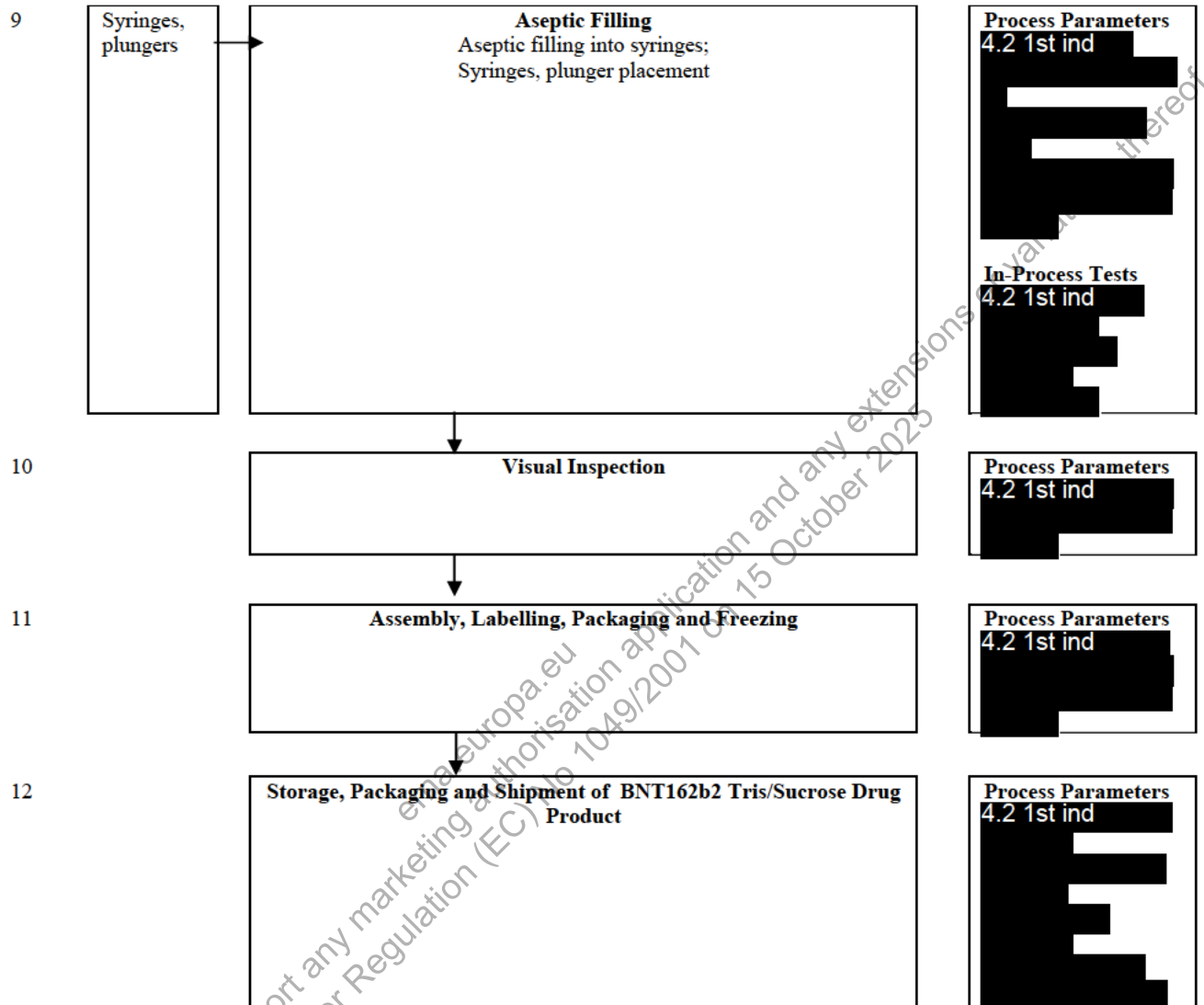
3.2.P.3.3.1. Flow Diagram

The process flow diagram for the BNT162b2 PFS fill and finish process is presented in [Figure 3.2.P.3.3-1](#)

Figure 3.2.P.3.3-1. Flow Diagram of the BNT162b2 Tris/Sucrose Drug Product Fill and Finish Manufacturing Process and Process Controls



090177e1a2a7d61fApproved\Approved On: 20-Jan-2025 09:42 (GMT)



a. This is an optional process step applicable 4.2 1st ind

b. The bulk drug product can optionally be split into two sublots.

Abbreviations: IPT-C = in-process test for control; IPT-M = in-process test for monitoring, DPI = Drug Product Intermediate

3.2.P.3.3.2. Drug Product Formulation Process Description

3.2.P.3.3.2.1. Thawing and Pooling of Tris/Sucrose Drug Product Intermediate

If an 0.5 mg/mL Tris/Sucrose drug product intermediate is used, the flexible freeze and thaw bags are first thawed and pooled. The Tris/Sucrose DPI (0.5 mg/mL) can be thawed either by using controlled thaw equipment (thawing chamber) or at controlled room temperature between 15-25 °C.

The process parameters for thawing of the DPI are provided in [Table 3.2.P.3.3-1](#).

Table 3.2.P.3.3-1. Process Parameters for Thawing of the Tris/Sucrose DPI

Process Parameter	Acceptable Range
4.2 1st ind	

The thawed drug product intermediate is transferred into a preparation vessel. The volume of the drug product intermediate in the preparation vessel must be within the validated batch size range for fill and finish operations.

3.2.P.3.3.2.2. Dilution of Tris/Sucrose Drug Product Intermediate to 0.1 mg/ml

After thawing and pooling of the Tris/Sucrose DPI, the intermediate is diluted with 300mM Sucrose, 10 mM Tris solution.

Up to 4.2 of Tris/sucrose DPI, containing 0.5 mg/mL of RNA, can be further diluted to a target concentration of 0.1 mg/mL RNA based on the calculation used in the previous dilution step (Concentration Adjustment with 4.2 sucrose, 10 mM Tris solution and Tris buffer, pH 7.5 and Addition of Cryoprotectant), to achieve a maximum final bulk drug product volume of approximately 4.2 1st ind.

The weight of 300 mM sucrose, 10 mM Tris solution required to achieve a target concentration of 0.1 mg/mL RNA is added. The solution is mixed until homogeneous.

The process parameters for the second concentration adjustment step are summarized in Table 3.2.P.3.3-2.

Table 3.2.P.3.3-2. Process Parameters for Second Concentration Adjustment Step to 0.1 mg/ml

Process Parameter	Acceptable Range
4.2 1st ind	

3.2.P.3.3.3. Fill and Finish Process Descriptions

3.2.P.3.3.4. Sterile Filtration

The final bulk drug product (0.1 mg/mL RNA) is sterile filtered into one or two holding vessels maintained at 2-8 °C. The bulk drug product can optionally be split into two sublots. The drug product is sterile filtered into two holding vessels 4.2 1st ind.

. The bulk drug

product suspension is filtered using 4.2 1st ind sterilizing grade filters. Refer to Table 3.2.P.3.3-3 for a description of the sterilizing filters. 4.2 1st ind

A sample is taken for bioburden 4.2 1st ind

The filters are flushed prior to use with 10 mM Tris buffer, pH 7.5, 10 mM Tris 300 mM sucrose solution or Water for Injection (WFI). Integrity of these filters is confirmed by pre- and post-use integrity testing. The wetting agents available for pre- and post-use integrity testing are 10 mM Tris buffer, pH 7.5, 10 mM Tris 300 mM sucrose Buffer, WFI 4.1(b). In addition, the post-use integrity test of the filters can be performed with bulk drug product as the wetting agent. At least one sterilizing filter is required to pass both pre- and post-use filter integrity tests. These in-process tests are included with the output process controls in Section 3.2.P.3.4 In-Process Monitoring and Controls – Fill and Finish –PFS (Frozen, Plastic) [Puurs].

The sterile filtration time cannot exceed the maximum time as determined by the bacterial retention filter validation and membrane compatibility studies as discussed in Section 3.2.P.3.5 Sterilizing Filter Membrane Validation – Sartorius - Tris-Sucrose.

The process parameters and IPT-C for sterile filtration are summarized in Table 3.2.P.3.3-3 and Table 3.2.P.3.3-4.

Table 3.2.P.3.3-3. Material Attributes and Process Parameters for Sterile Filtration

Material Attributes and Process Parameters	Acceptable Range	
	4.2 1st ind Filter	4.2 1st ind Filter
Filter pore size and membrane material of construction	4.1(b)	
Effective surface area per filter		
Filtration time		
Filtration pressure		

Abbreviations: 4.1(b)

Table 3.2.P.3.3-4. IPT-C Tests for Sterile Filtration

In-process Test	Acceptance Criteria
Pre-use filter integrity ^a	Pass
Post-use filter integrity ^a	Pass
Bioburden (pre-sterile filter)	4.1(b)

a. As the filtration step uses redundant filters, only one of the two filters is required to pass both pre- and post-use filter integrity tests.

3.2.P.3.3.5. Preparation of Syringes and Plunger Stoppers

The syringe barrels and plungers are supplied sterile and ready for use. The container closure system is described in detail in Section 3.2.P.7 Container Closure System – PFS.

3.2.P.3.3.6. Aseptic Filling and Plunger Placement

4.2 1st ind

The sterile bulk drug product in the holding vessel is aseptically connected to the filling line and then aseptically filled into syringes. During filling operations, the syringes are 4.2 1st ind filled and fully sealed with plunger stoppers. The 4.2 1st ind and 4.2 1st ind in-process tests are included in the output process controls. Table 3.2.P.3.3-5 shows the 4.2 1st ind. The IPT-C for the 4.2 1st ind are detailed in Table 3.2.P.3.3-6.

Table 3.2.P.3.3-5. Process Parameters for Aseptic Filling

Process Parameter	Target
4.2 1st ind	

Table 3.2.P.3.3-6. IPT-C Test for Aseptic Filling

In-process Test	Acceptance Criteria
4.2 1st ind	

During filling, in-process 4.2 1st ind testing are performed at routine intervals. This periodic check is performed to detect systematic errors related 4.2 1st ind

All non-conforming syringes are rejected. At the end of aseptic filling, a plunger is fully seated onto each filled syringe. During filling operations, plunger placement is checked at set time frames 4.2 1st ind. Furthermore, a 100% check on the presence and position of the plunger is performed during inspection.

Additional process control for aseptic filling is summarized in Table 3.2.P.3.3-7.

Table 3.2.P.3.3-7. Additional Process Control for Aseptic Filling

Process Control	Acceptable Range
4.2 1st ind	

These in-process tests performed in this step are included with the output process controls in Section 3.2.P.3.4 In-Process Monitoring and Controls – Fill and Finish –PFS (Frozen, Plastic) [Puurs].

3.2.P.3.3.7. Visual Inspection

Syringes are 100% inspected for defects either through automated visual inspection or manual visual inspection.

For automated inspection, prior to each batch, a challenge set of syringes is run through the machine to confirm that the detection systems are reliably detecting defective syringes and that the reject mechanisms are functioning properly.

During the 100% automated inspection process the syringes are fed to the inspection machine. The syringes undergo a check for plunger presence/position, particulate defects, container integrity, flange, barrel and cosmetic defects. The rejected syringes are segregated in pre-labeled reject tubs. The acceptable syringes are transferred to tubs.

If required, syringes may undergo 100% manual visual inspection. Syringes are manually inspected for missing/dislodged tip caps, plunger stopper presence/position, particulate defects, cosmetic defects, flange, barrel, and fill level defects. The plungers are inspected for presence, proper position, seal imperfection, liquid between the plunger stopper and plunger stopper defects. All rejected syringes are segregated into pre-labeled reject trays. The remaining acceptable syringes are placed into tubs or trays.

Syringes passing automated or manual inspection are statistically sampled for meeting acceptable quality limits. Throughout the inspection process, samples are taken for Acceptance Quality Limit (AQL) testing. Defects are classified as Critical, Major or Minor and addressed according to site procedures.

3.2.P.3.3.8. Assembly, Labeling, Packaging and Frozen Storage

The assembly, labeling and packaging of the BNT162b2 drug product PFS for commercial distribution is performed on a fully automated or semi-automated packaging line.

Inspected syringes are provided with a plunger rod and are individually labeled with a syringe label. Printers of the syringe labeler are used to print batch-specific information on the syringe labels. The line has integrated electronic verification systems, which electronically verify printed variable data and perform checks for label presence.

After assembly and labeling, the syringes are collected in cartons, using an automated tray or a manual tray process. After filling of the boxes, syringe quantities are verified, an insert may be added and the boxes are manually closed and labeled.

Packaged BNT162b2 syringes are frozen and stored in a freezer at -90 °C to -60 °C pending shipment for commercial distribution.

Alternatively, inspected syringes can be stored in a freezer at -90 °C to -60 °C prior to assembly, labelling and packaging activities.

The process parameter for freezing is summarized in Table 3.2.P.3.3-8.

Table 3.2.P.3.3-8. Process Parameter for Frozen Storage

Process Parameter	Acceptable Range
Freezing temperature	-90 to -60 °C

3.2.P.3.3.8.1. Storage, Packaging and Shipment of BNT162b2 Drug Product

Drug product syringes are stored according to conditions supported by the stability data detailed in Section 3.2.P.8.1 Stability Summary and Conclusions – Bivalent [Original and Omicron (BA.4-BA.5) Variant]-PFS (Frozen, Plastic) and Section 3.2.P.8.1 Stability Summary and Conclusions – [Omicron (XBB.1.5) Variant] – PFS (Frozen, Plastic).

Drug product is shipped under validated, primary qualified shipping conditions of -90 to -60 °C, as detailed in Section 3.2.P.3.5 Shipping Validation – PFS (Frozen, Plastic).

When drug product is shipped at -90 to -60 °C, the boxes containing the syringes are moved from the freezer, enclosed in a protective layer and placed into validated shippers that use dry ice for temperature-control. Temperature monitoring devices are inserted and activated for all shipping containers. Temperatures during shipment are verified to ensure that the product is maintained at -90 to -60 °C. Drug product may be shipped to qualified distribution centers or logistics service providers for temporary storage and deconsolidation into smaller bundles or quantities for continued shipment. Established conditions for product handling, redistribution and storage during transport have been established, as detailed in Table 3.2.P.3.3-9.

The product temperature in the shipper can be maintained by adding additional dry ice. Alternative insulated thermal conveyances may be used following appropriate qualification.

Process parameters for product handling, redistribution and storage during transport are summarized in Table 3.2.P.3.3-9.

Table 3.2.P.3.3-9. Process Parameters for Product Handling, Redistribution and Storage During Transport

Process Parameter	Acceptable Range
4.2 1st ind	

Additionally, shipping and temporary storage in the thermal conveyance containing dry ice at temperatures as cold as -98 °C are not considered excursions and are supported by the container closure integrity data presented in Section 3.2.P.2.4 Container Closure System – PFS.

3.2.P.3.3.9. Hold Times

The hold times of the drug product in-process materials during sterile filtration, filling and inspection are provided in Table 3.2.P.3.3-10 for PFS (Frozen, Plastic).

Table 3.2.P.3.3-10. Fill and Finish Process Hold Times

Material or In-Process Hold Description	Process Steps	Target Hold Time
Liquid drug product in vessels or plastic syringes at 2 to 25°C.	Cumulative time in vessels or plastic syringes at 2-8°C from the start of concentration adjustment and cryoprotectant addition until the start of freezing, including time held in stainless steel vessels, thawing of DPI, pooling of DPI, dilution of DPI, sterile filtration, filling, inspection, and secondary packaging, with ≤ 72 hours of this time allowed up to 25 °C	4.2 1st ind

- a. Sterile filtration time limited based on microbial retention study; fill hold time limited based on media fill study.

3.2.P.3.3.10. Reprocessing

A single refiltration of bulk drug product through the sterile filtration step may be performed in cases where the sterilizing grade filter fails to meet the post-use integrity test or if a technical issue compromises the integrity of the system. The refiltration is performed using new, identical 4.2 1st ind sterilizing filters. An out-of-limit bioburden result will preclude a refiltration step.

A bioburden sample will be taken prior to refiltration with acceptance criterion of 4.2 1st ind and new filters must pass the pre-and post-use integrity tests, as summarized in Table 3.2.P.3.3-4. If reprocessing is required, the hold time limits described above still apply.