8.0 Packaging and Sterilization

OP-1 Implant Terminal Sterilization Process and Controls

Overview

At the Stryker Biotech, West Lebanon, NH facility, OP-1 Implant material is dispensed into 2 ounce vials, the vials are half-stoppered, placed into a vacuum chamber (lyophilizer) where the headspace is evacuated and the stoppers are fully seated under vacuum. The vials are crimp-sealed with gamma stable plastic/aluminum seals and labeled with lot number and Stryker Biotech artwork. Crimped vials are individually placed into thermoform trays, which are heat sealed with Tyvek® covers.

The packaged OP- 1 Implant units are then packaged for irradiation, and shipped from West Lebanon, NH to Steris-Isomedix, Northborough, MA where they are terminally sterilized using gamma irradiation (^{60}Cobalt source of irradiation). Sterilized OP-1 Implant units are then shipped to Stryker Biotech, Hopkinton, MA where they are received and inspected. The irradiation documentation is also reviewed for completeness and conformance to in-process control specifications. Units are stored in quarantine at refrigerated temperature pending release testing. Released product is then labeled and packaged along with putty additive as OP-1 Putty for storage and distribution.

Refer to Section I of this PMA for Steris-Isomedix MAF authorization letter.

Process Description

Terminal Sterilization Process

Insulated containers containing packaged OP-1 Implant and refrigerant packs are shipped to Steris-Isomedix, Northborough, MA. Upon arrival at Steris-Isomedix, the closed insulated containers are held at ambient temperature in the warehouse. When ready for irradiation, the cases of OP-1 Implant are removed from the insulated shipping containers and placed into aluminum carriers. The aluminum carriers are connected to the overhead monorail conveyor system which presents the cases to the irradiation source. A minimum of six dosimeters (with one used as reference) are utilized to record the dose received at the previously determined minimum dose and maximum dose locations. While the OP-1 Implant units are being sterilized, the shipping containers are closed to maintain the temperature of the refrigerant packs.

When all carriers are positioned in the irradiation cell, the ^{60}Cobalt source is raised into the processing position and the carriers automatically conveyed and rotated around the source until the target kilogray (kGy) dose is achieved.

The minimum and maximum radiation dose range for OP-1 Implant is 24.5 kGy to 31.5 kGy. The minimum target dose required to achieve a 10^{-6} Sterility Assurance Level (SAL) for OP-1

Implant was determined by validation studies to be 24.5 kGy. The delivery of a consistent dose in the range of 24.5 kGy to 31.5 kGy has been validated by means of dose mapping. A target dose was selected that assured all locations within the carrier achieve greater than the minimum dose. A more detailed discussion of the validation of this process is the presented in Section **Error! Reference source not found.**.

Upon completion of the sterilization run, the product cartons are removed from the aluminum carrier and are placed back into the shipping container while the run dosimeters are evaluated. These dosimetric measurements are traceable to and consistent with national standards of absorbed dose by means of reference or transfer dosimeters. After Steris-Isomedix has verified that the minimum and maximum radiation dosages are within specification, the containers are shipped to Stryker Biotech, Hopkinton, MA. The entire processing step, from packaging of the product shippers in insulated containers by Stryker Biotech, West Lebanon, NH facility to final delivery and storage of the irradiated product at the Stryker Biotech, Hopkinton, MA facility must take place within 72 hours.

Upon receipt at the Stryker Biotech Hopkinton facility, the product shippers are removed from the shipping containers and placed into the 2° to 8°C quarantine area. The product is sampled per documented procedures. Product is held until all quality requirements have been satisfied, including the in-process specifications shown in Table 11-2. The maximum time between packaging and sterilization of the lot is 21 days. The irradiation dose delivered to all dosimeters is within the range of 24.5 kGy to 31.5 kGy. Full details of the final release testing may be found in Volume 7. See Table 11-2 for irradiation in-process specifications.

Table 11-2: Irradiation In-Process Control Specification

Parameter	Range
Hold Time (from packaging to sterilization)	≤ 21 days
Dose Range	24.5 kGy to 31.5 kGy
Dwell Time	1.5 to 3.0 hours

Routine sterilization audits are performed once every three months (quarterly) during production. Ten units are selected from one OP-1 Implant lot prior to irradiation and tested for bioburden. An additional ten units are selected, irradiated at a lower dose and then submitted for subprocess dose verification (VDmax method based on AAMI TIR 27:2001). See Table 11-3.

Table 11-3: Quarterly Sterilization Audit Testing

Test	Acceptance Criteria
Bioburden	≤ 1.6 MPN per Vial
Subprocess Dose Sterility Test	≤ 1 Positive Vial

Bioburden – Test Method Description

Pre-irradiated OP-1 Implant is evaluated for bioburden as part of quarterly dose audit testing. The bioburden test uses a modification of the standard replicate tube method.[i] The method estimates the microbial concentration as a most probable number (MPN) of bacteria by counting the number of vials, out of 10, which are positive for growth. The number of positive vials is compared to a standard table to arrive at the estimated concentration of microorganisms. The table of most probable numbers is derived from Clesceri et al.[i]

To perform the test, 10 vials (pre-irradiation) are selected from an OP-1 Implant lot. A minimum of 20 mL Trypticase Soy Broth (TSB) is aseptically added to each vial. All the vials are incubated at 28° to 32°C for minimum of 14 days. Turbidity in the media in the vial is indicative of growth. The number of vials with growth is compared to a table of most probable numbers. The test range is < 0.1 MPN (0 positive vials) to 2.3 MPN (9 positive vials) per vial of OP-1 Implant.

Representative isolates from any vial positive for growth are identified at minimum to the genus level. The level of any known gamma irradiation-resistant microorganisms is assessed to ensure that the levels present do not exceed those found in the original product sterilization validation.

Validation of the method followed the guidance of USP <1227> and included performing two tests: a test for method accuracy, and a test for bacteriostasis / fungistasis. The validation report is provided in Appendix 11-A.

Subprocess Dose Sterility Test - Test Method Description

The subprocess dose audit experiment requires ten units of OP-1 Implant, pre-irradiation. The ten vials are irradiated at the subprocess dose that was determined during the sterilization validation. Following irradiation each of the ten vials is tested for sterility by adding a minimum of 20 mL trypticase soy broth (TSB) directly to the vials. The vials are then incubated at 28° to 32°C for a minimum of 14 days. Per AAMI TIR27:2001, the test passes if there is no more than a single vial positive for microbial growth.

At the end of the incubation period, vials which are negative for microbial growth are selected for a growth promotion test. Control levels of microorganisms are added to the vials to demonstrate that the medium supports growth and that there is no bacteriostasis or fungistasis. This system suitability check ensures that each sterility test is valid.

Control of Materials

OP-1 Implant is packaged in 2 oz vials (USP Type 1 borosilicate glass) and sealed under vacuum using a 43 mm 4416/60 gray butyl pre-siliconized stopper. The target fill for the vials is 1.05 grams of OP-1 Implant per vial. The vials are packaged into thermoformed blister trays and terminally sterilized by gamma-irradiation.

Primary Packaging

A list of the primary packaging materials is presented in Table 11-4 below. Material specifications follow.

Table 11-4: OP-1 Implant Primary Packaging Materials

Description
2 oz. (16 Dram) Vial
Lyo Stopper, 43 mm
Flip Tear-off Seal 43 mm, Gamma Stable

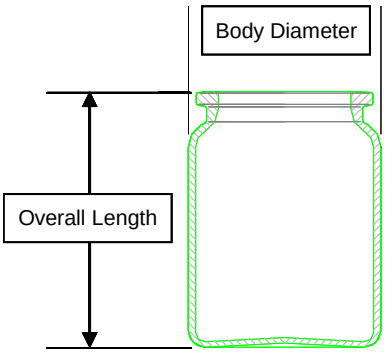
Container

OP-1 Implant is filled into 43 mm, 16 dram (2 ounce) Type I borosilicate glass tubing vials manufactured by Schott Glaskontor, Mulheim, Germany. An authorization letter for the DMF is located in Section I. The specifications are presented in Table 11-5 and a drawing is provided in Figure 11-3.

Table 11-5: Specifications for 2 oz. Vial

Attribute / Test	Specification	Reference
Visual	Pallet acceptable	Visual Inspection
	Certificate of Conformance present Glass transparency color conforms to Standard	COC
	No Full length scratches. No signs of damage i.e. cracks, chips, broken units. No signs of deformities to glass (i.e. distorted vial necks, extra glass globules and or protrusions. stars and/or bulls eyes. No gas bubbles/foreign matter inclusion >0.5 mm O.D. Surface Banding acceptable.	Tappi Std.
Dimensional Inspection (All dimensions in Millimeters see drawing for dimension locations.)	Crown O.D. 41.25 ± 0.75 Bottom Thickness > 1.3 Neck I.D. 31.00 ± 0.25 Overall Length 60.00 + .40/- .70 Body Diameter 45.00 ± 0.80 Bottom Angle < 0.64 TIR	Calipers/Optical Comparator
Vials for prewashing	Submitted to Parts Prep.	Washed vials submitted for USP and EP testing
Identity: USP/EP Type I Borosilicate Glass	Current USP <661> Current EP 3.2.1, - Arsenic Test - Surface Hydrolytic Resistance Test - Hydrolytic Resistance of Powdered Glass Test	Washed vials submitted for USP and EP testing to NAMSA or Monarch or other approved test lab

Figure 11-3: Drawing for 2 oz. Vial



[i]. Clesceri LS, Greenberg AE, Eaton AD. *Standard Methods for the Examination of Water and Wastewater*. 20th ed. American Public Health Assoc, American Water Works Assoc., Water Environment Federation. 2005:9:51-53.