PACKAGING AND SHELF LIFE
Submission 2003/098

PIP's high cohesivity silicone gel filled breast implants are individually packaged in a double packaging system that consists of a transparent polyethylene film overlaying a polypropylene box. This external box forms a protective barrier around the inner double PETG moulds. The external PETG blister with a Tyvek lid carries an identification label (as discussed in the Labelling and Instructions for Use Report) as well as the three self-adhesive patient labels. The internal PETG blister mould has a protective indent to hold the implant.

General

Packaging assembly is described in the report MET 02/001 (Volume 17) and the various tests performed to qualify the packaging in paragraph of IV.4 of that report. The tests include

- uniformity of sealing the blisters and lids
- an air tightness test for the sealed thermoforms (dye penetration and bubble emission)
- seal integrity test (mechanical peel test)
- peel test.

MET 02/001 identifies a number of standards and documents that are critical to the packaging choice, production and qualification.
MET 02/001 identifies and provides contact details of the suppliers of the packaging components, packaging specifications.

Validation of seals

a) Continuity and uniformity of seals
The purpose of this test is to assess the seal uniformity using an UV light at 365nm.
PETG blisters and lids are sealed under the standard conditions of heat (120^0C) and pressure (6 bars). Time of heat and pressure application is varied from 1 to 4 seconds. Three samples are tested per each test time.

Below 3 seconds the seals in each case were not satisfactory, cloudy, white and with bubbles. At three seconds application of heat and pressure the seals were uniformly continuous exhibiting an intense blue colour.

b) Colour penetration & bubble emission –
(i) outside to inside
This test is designed to evaluate the imperviousness of the seal from outside to inside. Sealed blisters (as described above) are immersed with the lid side down in methylene blue solution for 15 minutes, followed by rinsing under running water. If the residual dye has not managed to diffuse across the seals in 24 hours they can be determined as watertight.

Below four seconds methylene blue infiltrations into the seal can be observed. Sealing for 4 seconds excludes the infiltration of dye.

(ii) inside to outside
This test is based on ASTM F 1929 (1998) and consists of injecting a solution of 0.05% Toluidine blue / Triton X-100 at 0.05% in water into the sealed blister so that the solution is in contact with each seal for a period of 20 seconds. The seal is defined as being impervious as there is no infiltration of the dye during the 20 seconds of exposure.

Below four seconds toluidine blue infiltrations into the seal can be observed. Sealing for 4 seconds excludes the infiltration of dye.

(iii) bubble emission
This test demonstrates watertightness of the seals when the sealed package is immersed in water with application of vacuum to 0.8 fir 30s to the system followed by exclusion of water in the package on release of vacuum.

Sealing for 4 seconds prevents bubble emission and penetration of water.

c) Mechanical peel test
Tensile testing equipment is used to assess the force required to peel the lid from its seal with the PETG thermoform. A four-second application of the standardised sealing temperature and pressure are used on the test articles. Maximum, minimum and average force of peel are determined and used to calculate the tear resistance.

Test article: Forces
Minimum: 0.15kN/m
Maximum: 0.38kN/m

Specifications from NF EN 868-10 are adopted.
Minimum: 0.08KN/m
Maximum: 1.00kN/m

d) Manual peel test
The package is sealed using standardised temperature and pressure conditions for 1, 2, 3 or 4 seconds. Criteria are a) ease of opening (no lid resistance and tear)
b) sealing zone uniformity

Observations against these criteria revealed that only sealing at 4 seconds provided the correct uniform seal and no tear.

Report MET 03/013 analyses results of mechanical peel testing of the inner and outer blister seals for five product lots before and after sterilisation with ethylene oxide. This test is performed routinely on a four-month cycle. For both inner and outer blister seals the mean results for before and after sterilisation are not significantly different and comply with all specifications.

The microbial barrier properties of these seals will not be discussed here as that topic is dealt with elsewhere in the dossier report.

The operational SOP for blister packing, FFA 220/01 specifies the following settings

Sealing temperature	120^0C
Sealing pressure	6 bars
Sealing time	4 seconds

The specifications given for this operation are satisfactory.

Qualification of the physical protective capacity of the packaging

The dossier summarises the elements that contribute to capacity of the packaging materials to adequately protect the medical device during handling, transport and storage. For example the device is not exposed to any sharp areas in the primary or secondary packaging which are constructed from PETG of adequate strength and hardness to resist impact. The third layer, PP box provides additional protection against damage, impact and penetration that may compromise the integrity and sterility assurance of the product.

Three samples taken from the stability protocol at 21 months (2002) were subjected to the rigors of transportation from France to Seoul and return and subsequently tested for

- Sterility and pyrogenicity on 1 implant - results: sterile and apyrogenic
- Tests on the packaging and implant on 2 implants – all seals conform, mechanical and visual properties conform

Two samples taken from the stability protocol at 38 months (2003) were subjected to rigors of transportation from France to Seoul and return and subsequently tested for

- Packaging – all seals conform
- Implants - mechanical, visual properties and sterility conform

The manufacturer has performed testing and provided evidence that the packaging is capable of ensuring product integrity and maintaining sterility when challenged with >3 storage at 20^0C followed by air transport of approximately 10,000Km

This is satisfactory.

STABILITY

P.I.P. established a Validation Protocol for 5-year expiration of the ethylene oxide sterilised blister packaged breast implants. The stability protocol comprised 7 parts:

a) presentation of validation protocol
b) risk analysis to be considered in terms of the stability study; the following in put will be considered – in broad terms:
   (i) Chemical criteria
   (ii) Physical criteria
   (iii) Microbiological criteria
   (iv) Toxicological criteria
   (v) Biocompatibility
   (vi) Packaging criteria
c) packaging performance
d) packaging integrity at post sterilisation phase
e) review of mechanical properties of breast implants after ethylene oxide sterilisation
f) in put of factors that may influence shelf life.
g) Purpose to validate 5 year expiry date

The study plan is comprehensive and rigorous. Furthermore provides details of the verification plan for the described protocol, with the study concluding in 2006. The planned verification tests commenced at the end of 2003, early 2004.

RECOMMENDATION

The manufacturer should be requested to submit the Final Study Report for Stability Verifying the 5-year Shelf Life at the study's conclusion.

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