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To: Medical Devices Stakeholders

Subject: Preparation of a Premarket Review Document for Breast Implant and Tissue Expander Applications

The *Medical Devices Regulations* set out the requirements governing the sale, importation and advertisement of medical devices. The goal of the Regulations is to ensure that medical devices distributed in Canada are safe and effective and meet quality standards. These Regulations were published in *Canada Gazette II* on 27 May 1998, and implementation began on 1 July 1998.

This document, entitled *Preparation of a Premarket Review Document for Breast Implant and Tissue Expander Applications*, sets out the Programme's guidance for Industry on the subject.

This guidance document is to be used in the preparation of Class IV medical device licence applications and licence amendment applications, in compliance with the licensing provisions in section 32 of the *Medical Devices Regulations*. Licence applications for breast implants and tissue expanders will require a scientific and medical review of submitted evidence of safety and effectiveness before their licence applications can be finalized.

For more information on how to prepare a premarket review document for breast implant or tissue expander device licence applications, please contact any of the following:

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Attachments

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Therapeutic Products Programme

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Therapeutic Products Programme
GUIDANCE DOCUMENT

Preparation of a Premarket Review Document for Breast Implant and Tissue Expander Device Licence Applications

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Document Change Log

Document Number	GD017/Rev00-MDB	**Replaces**	GD016/RevDR-MDB
File name	tpp_breast_update.wpd	**Replaces**	tpp_breast.wpd
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Change	Location	Nature of Change
1	**Title Page, Document Number.**	Document control number changed, so as not to be confused with the discontinued guidance document GD016. Document is no longer draft.
2	**Entire Document**	Minor editorial and style changes.
3	**4.1.2 Chemical Analysis**	Cryogrinding is not recommended for sample preparation.
4	**5.1 Preclinical Testing**	Clarification regarding the testing of the thinnest possible samples, alternate methods may be required. Applicability of joint testing with domed or button valves discussed. Fold Flaw testing no longer required. Abrasion testing no longer required. Fatigue rupture testing to include stress calculations, and a recommendation to use load controlled apparatus.
5	**5.2 Clinical Testing**	Consideration given to further subdividing reconstruction patients into reconstruction and augmentation sub-groups. To take into account the previous overall health history of the patient. Breast cancer patients are excluded from the long term reconstruction study population.
6	**5.2.2 Safety Assessment**	Discussion around MRI follow studies has been expanded. Basic definitions provided. Prospective collection and preservation of serum (or plasma) samples is not required. Collection and testing of serological samples as recommended during scheduled follow-up visits is still required.

Table of Contents

1.0 Introduction

1.1 Purpose

This is one of a series of guidance documents issued by the Therapeutic Products Programme (TPP) to inform manufacturers of safety and performance criteria for certain therapeutic products. TPP considers these criteria to be a reasonable interpretation of the minimum safety and effectiveness requirements which a product must meet in order to satisfy applicable regulations under the Food and Drugs Act.

1.2 Background

The *Medical Devices Regulations* stem from the 1992 report of the Medical Devices Review (Hearn) Committee. The report advocated two principles: (1) The level of scrutiny afforded a device should be dependent upon the hazard that the device presents; and (2) The safety and effectiveness of the device can best be assured through a balance of quality systems requirements, premarket scrutiny and postmarket surveillance.

One quarter of licensed medical devices sold in Canada are Class IV. These devices pose the greatest hazard to the Canadian public, and therefore will undergo a detailed review of safety and effectiveness information.

For the purpose of obtaining a medical device licence, a manufacturer may propose an alternate means of establishing safety and effectiveness, but the burden of proof required to establish the acceptability of the alternate means rests with the manufacturer. A licence will not be issued until the manufacturer can provide sufficient evidence to Health Canada to establish that the alternate methods or standards used are equivalent to or better than the information and tests referred to in this policy.

1.3 Scope

This guidance document describes the safety and effectiveness information that TPP will use to determine compliance with Section 32(4)(f) to (i) and (o) of the Medical Devices Regulations. The reader is referred to the general guidance document “Preparation of a Premarket Review Document for Class III and Class IV Device Licence Applications” for discussion of how to meet Sections 32(4) (a) to (e), (l), (n) and (p) of the Regulations.

This document discusses information relevant to breast prostheses filled with silicone gel, saline, or alternative filler intended for breast augmentation, breast reconstruction following mastectomy, and revision of a failed prosthesis. This guidance also addresses tissue expanders, which may be for temporary use. This guidance does not address the requirements for alternative shell materials for use in breast implants. Manufacturers of such products are advised to contact the Programme.

The evidence to be submitted for review is in addition to the general data elements listed in section 32, subsection (1), paragraphs (a) to (e), which are necessary for all medical device licence applications.

An amended licence application must contain all the relevant information to support the safety and effectiveness of the modified device.

1.4 Definitions

Additional Information refers to a written request made under section 35(1) for ADDITIONAL INFORMATION necessary to determine whether a medical device meets the safety and effectiveness requirements for a particular licence application.

Breast Implant - a breast prosthesis filled with either silicone gel and/or saline or both, or an alternate filler intended for breast augmentation, breast reconstruction following mastectomy, and revision of a failed prosthesis.

Silicone inflatable (saline-filled) breast prosthesis - A silicone inflatable (saline-filled) breast prosthesis has a silicone rubber shell made of polysiloxane(s), such as polydimethylsiloxane and polydiphenylsiloxane, that is inflated to the desired size with sterile isotonic saline before or after implantation. Most of these prostheses are single lumen devices with a valve that is sealable by the surgeon or self-sealing for the purposes of filling the prosthesis. The implants have a patch that covers the manufacturing port of the prosthesis. There are two types of saline-filled prostheses. One type is a fixed volume prosthesis, which is filled with the entire volume of saline at implantation. Another type is an adjustable volume prosthesis, which is filled intraoperatively and has the potential for further postoperative adjustment.

Silicone gel-filled breast prosthesis - Silicone gel-filled breast prostheses are sub-classified by their number of lumens. Each implant has a patch that covers the manufacturing port of the prosthesis.

A single-lumen silicone gel-filled breast prosthesis has a silicone rubber shell made of polysiloxane(s), such as polydimethylsiloxane and polydiphenylsiloxane. The shell contains a fixed amount of silicone gel.

A double lumen silicone gel-filled breast prosthesis is a silicone rubber inner shell and a silicone rubber outer shell, both shells made of polysiloxanes(s), such as polydimethylsiloxane and polydiphenylsiloxane. One shell contains a fixed amount of silicone gel. A valve or series of valves allows for filling of the other shell with saline at the time of implantation and also allows for postoperative volume adjustments to be made.

A tri-lumen silicone gel-filled breast prosthesis incorporates a separate gel-filled core within a gel-filled lumen, both surrounded by an outer shell designed to be filled, generally, with physiological saline.

Alternative breast prosthesis - Typically, an alternative breast prosthesis has a silicone rubber shell whose filler contains any material other than saline or silicone gel. The filler material may or

may not be a gel. However, an alternative breast implant may also have an alternative shell other than that made from silicone rubber. The sponsor is advised that additional information other than that described below may be necessary for alternative shell breast implants.

Tissue Expander - an implanted prosthesis intended for temporary use which has the potential for postoperative adjustment. These devices may contain saline alone or in combination with silicone gel or other alternate filler material.

Masterfile refers to a document provided by a subcontractor or manufacturer that contains specific objective evidence, for example material characterization or sterilization processing characteristics. This data is often independent of final device processing and can be referenced by many different device licence applications. If the file has been submitted by someone other than the manufacturer, permission must be granted in writing by the file owner for each licence application using the information contained in the MASTERFILE.

2.0 Procedures

The document *Guidance on How to Complete the Application for a New Medical Device Licence* (GD013/Rev00-MDB) contains detailed information on submitting a device licence application to TPP for all Class II, Class III and Class IV devices.

A new licence application for a Class III or a Class IV medical device will contain a premarket review document in addition to the general requirements of section 32(1). Portions of the review submission may reference a MASTERFILE already submitted by the manufacturer or a subcontractor.

Under section 35(1) of the *Medical Devices Regulations*, if the information or documentation submitted in respect of the licence application under section 32 is insufficient to determine whether the device meets the safety and effectiveness requirements of sections 10 to 20, then a manufacturer may be requested in writing to submit ADDITIONAL INFORMATION.

In the event of a significant change, an amended licence application is required. This amended device licence application will include the information set out in section 32 that is relevant to the change. It is not necessary to resubmit safety and effectiveness data that has not been affected by the change. This application must be reviewed and accepted before the altered device is offered for sale. Manufacturers are referred to the *Guidance Document for Significant Change*, document number GD001/Rev-MDB, for further details.

A licence or a licence amendment will be issued if the Minister, after reviewing the information included in the licence application or licence amendment application, determines that a medical device conforms to the safety and effectiveness requirements.

This guidance document provides information for regarding the premarket documentation required for breast implant or tissue expanders. Manufacturers and/or device sponsors with general

questions or concerns regarding the device licensing process are urged to consult the document *Policy on the Management of Applications for Medical Device Licences or Authorizations for Investigational Testing* or contact the Manager, Device Licensing Services Division, Medical Devices Bureau at (613) 957-7285.

3.0 Access to Information Act and the Confidentiality of Licence Applications

Information provided to the Programme by manufacturers and/or device sponsors is subject to the provisions of the *Access to Information Act*. Application information containing trade secrets or confidential scientific, technical, commercial or financial information is protected from disclosure by this Act. According to TPP policy, information regarding device licence applications that have been received or are being processed is also considered confidential. Once a licence is granted, basic information about a device, such as that listed in section 32(1), is considered public information.

4.0 Safety and Effectiveness Requirements

4.1 Material Specifications

4.1.1 General Information

A complete list of all of the chemicals used in the manufacture of the breast prosthesis should be provided. The list should include the common names and trade names of each chemical component, the specific role of each chemical in the manufacturing process and/or in the final device. The location of the chemical within the device, e.g., in the shell, the inner or outer layers of the shell, in the filler, valve, or adhesive, should also be provided. Polymeric components should be described by chemical name, mean molecular weight, and a measure of the polydispersity. Material safety data sheets (MSDS) should be provided for each chemical.

4.1.2 Chemical Analysis of Elastomer Shell including Patch and Valve

Chemical analyses of the elastomer shell, including the patch and valve, should be provided. The elastomer should be analyzed separately from the filler. A suitable method of sample preparation should be used to avoid polymer degradation and volatile loss. The sample should be analyzed for volatile components. Changes in design features, such as texturing, variations of device components such as patches or valves, or changes in sterilization, may necessitate additional analyses to detect variations in chemical composition.

An analysis of the extractable or releasable chemicals of an implant is necessary for the assessment of the safety of the device. The identification and quantification of releasable chemicals should be provided to identify potentially toxic chemicals and estimate the upper limits of the chemicals that could be released to the patient.

The following is one option which may be followed to address this issue. The extraction of the shell for chemical analysis can be performed with at least one polar solvent (i.e. ethanol or a mixture of ethanol-water) and two non-polar solvents (i.e. dichloromethane and hexane). To determine the duration of the exhaustive extractions, a series of successive extractions can then be

conducted by exposing the sample to the solvent for a period of time, analysing the solvent for extractables, replacing with fresh solvent, again exposing the sample for a period of time, analysing, and repeating the process. When the level of the analyte for the extraction is one-tenth (0.1) the level in the previous extraction, the extraction is deemed complete so that a 10% correction to the total extractable material can be applied. In cases where this condition may not occur because of extremely slow migration of the higher molecular weight material, the test can be applied to the contents of the extract with molecular weights below 1500 because these are the compounds of greatest interest. All the separate analyte levels are then added together to calculate the cumulative value and, via the sample/solvent ratio, the sample and device levels. The total extraction from the polar solvent and the extraction from one of the non-polar solvents that yields the higher amounts of extractables should be used for both quantitative and qualitative analyses. Extracts that may contain oligomeric or polymeric species should have the molecular weight distribution provided, along with the number and weight average molecular weights and the polydispersity. Experimental evidence should be provided to show that exhaustive extraction has been achieved with one of the solvents. The percent recovery, especially for the polydimethylsiloxanes (D3 or D4), should be reported.

Chemicals below a molecular weight of 1500 should be quantified and identified after exhaustive extraction of the final sterilized device. The thresholds for identification and quantification of these compounds will depend both on their relative toxicity and their relative percent weight in the finished device. Manufacturers must justify their conclusions regarding the above tiered system of thresholds, and provide evidence regarding the % by weight of these low molecular weight compounds.

All experimental methodology (e.g., GPC, GLC/MS, GLC/AED, and FTIR) should be described. Raw data (including instrument reports) should be available upon request, along with all chromatograms, spectrograms, etc. The practical quantitative limit (PQL) (see "Compilation of EPA's Sampling and Analysis Methods," Lewis publishers, 1992) should be provided when the analyte of interest is not detected.

4.1.3 Chemical Analysis of Filler Materials

4.1.3.1 Saline

Normal physiological sterile saline has a long history of use in breast implants and is standardized by the USP. As stated above, the sterile saline to be used with the implant should conform to USP standards of Normal Physiological Saline (injection grade) which has a concentration of 0.15M and a pH of 7.2-7.4. If the breast implant is to be used with any other saline, then a complete chemical analysis of the saline should be provided.

4.1.3.2 Silicone Gel

The requirements for the analysis of the gel are similar to those for the elastomer shell. A detailed chemical analysis of the gel product should be provided, including both qualitative and quantitative analyses for volatiles, heavy metal contents, and extractables such as cyclic

polysiloxanes. This information should include identification of the polymers present, molecular weight averages and polydispersities of the polymers, and the identification and quantification of all compounds present with a molecular weight of 1500 or less.

4.1.3.3 Alternative Filler - Polymer

If the filler is a polymer material, the following information should be provided: rationale for the use of the specific alternative material; a list of all the components used in the synthesis and the method of synthesis of any polymer used in the preparation of filler (if it is a synthetic polymer) or the source of the polymer, if it is a natural polymer; the method of purification of the polymer; formulation of the polymer (the ratio of polymer should be specified if the filler material is a mixture of more than one component); structural analyses of the polymer, including molecular weight distribution; quantification and identification of all chemicals below a molecular weight of 1500, including the monomer and their characterization; trace metal/heavy metal analysis; cross-link density (if it is a synthetic and cured material), and; stability data.

Long-term stability and accelerated aging studies (at least to 45˚C) should be provided to demonstrate the effects of time and temperature on the physical properties and chemical composition of the device (filler and shell). Key physical parameters such as viscosity and cohesivity should be measured at each time point in the stability or aging study. If there are no mechanical changes, the levels of the major components should be measured, but if there are mechanical changes, complete chemical analyses should be conducted to explain the physical changes.

4.1.3.4 Alternative Filler – Non-Polymer

If the filler is a non-polymer material, the following information should be provided: rationale for the use of the specific alternative material; composition of the non-polymer, including characterization of smaller-molecular weight components; method of purification of the non-polymer; source of the non-polymer; the structural analyses of the non-polymer, including molecular weight distribution, and; stability data.

Long-term stability and accelerated aging studies (at least to 45˚C) to demonstrate the effects of time and temperature on the physical properties and chemical composition of the device (filler and shell) should be provided. Key physical parameters such as viscosity and cohesivity should be measured at each time point in the stability or aging study. If there are no mechanical changes, the levels of the major components should be measured, but if there are mechanical changes, complete chemical analyses should be conducted to explain the physical changes.

4.2 Manufacturing Process Specifications

4.2.1 Method of Manufacture

Complete manufacturing information must be submitted, including: specific chemical processing, sterilization and quality assurance information is required to assess the safety and effectiveness of silicone (saline) inflatable breast prostheses.

Manufacturing and process tree information which show how the components of a device are made from starting materials should be provided. This information would identify potentially leachable chemicals and immediate precursors of cross linked polymers. A complete master list of common chemical names and alternate names (company, trade and code) for all nonreactants, reactants (including intermediate precursors), additives, catalysts, adjuvants, and products should be provided. The same name for each specific compound must be utilized throughout the document.

4.2.2 Quality Control Activities

A QA/QC plan that demonstrates how raw materials, components, subassemblies, and any filling agents will be received, stored, and handled in a manner designed to prevent damage, mixup, contamination, and other adverse effects must be provided. This plan shall specifically include, but not necessarily be limited to, a record of raw material, component, subassembly, and filling agent acceptance and rejection, visual examination for damage, and inspection, sampling and testing for conformance to specifications.

Written procedures for finished device inspection to assure that device specifications are met must be provided. These procedures shall include, but are not limited to, that each production run, lot or batch be evaluated and, where necessary, tested for conformance with device specifications prior to release for distribution. A representative number of samples shall be selected from a production run, lot or batch and tested under simulated use conditions and to any extremes to which the device may be exposed. Furthermore, the QA/QC procedures should include appropriate visual testing of the packaging, packaging seal, and product.

Sampling plans for checking, testing, and release of the device shall be based on an acceptable statistical rationale.

4.2.3 List of Standards

Currently there are no standards recognized by TPP for breast implants or tissue expanders. ASTM F 703-96 Standard Specification for Implantable Breast Prostheses is referenced regarding its procedures for testing breast implants. Manufacturers may also reference EN 12180, in so far as it is equivalent to ASTM F703-96.

5.0 Safety and Effectiveness Studies

Breast implants are made in a variety of different designs. The basic components or design features of any breast implant are the shell, filler, and patch (or seal); optional components may include valves and/or adhesives. Breast implants may consist of single, double, or triple lumens. Preclinical testing is necessary to evaluate the material and mechanical properties of the specific breast implant under review.

Because the morphology and integrity of the materials and of the design features can be affected by processing, it is imperative **that all testing be performed on finished, sterilized total devices or components (e.g. shell, gel, and valve)**. If the device is to be sterilized by different methods (e.g.,

ethylene oxide, gamma radiation, etc.), then preclinical testing should be performed on samples sterilized by the different methods unless an adequate rationale is provided that the change in sterilization method does not negatively impact the mechanical characteristics. Additionally, for samples prepared from silicone-gel implants, there may be difficulty in performing the testing without cleaning, particularly with respect to testing jig grip areas. TPP suggests cleaning only the grip contact areas as described in ASTM F703 to remove the presence of silicone gel and oils.

Testing should be performed on representative models and/or sizes. For example, the sponsor may choose to test the worst case implant model and size or test a range of sizes within a given model; however, the rationale for the model(s) and size(s) tested should be provided. Additionally, when determining what is the worst case implant to test, the sponsor should use implants manufactured with the thinnest shells allowed by the design release criteria.

All testing should be performed to a pre-defined failure of the component. A statistically valid number of samples should be used in each test performed. Complete reports of the preclinical testing should include, at minimum, the following elements: identification of the components/devices tested including model and size, sample dimensions, etc. (again note that all testing should be conducted on the final, sterilized version); the test set-up and methods including schematic drawings; the rationale that testing involved the worst case design and size or, at least, that it involved one that was representative of the other implants under review, an explanation of how or why the results are relevant if there are differences between the proposed and tested implants in terms of material, design, or sterilization method; the results with standard deviations, as well as the raw data and failure modes/analysis; and a discussion of the results in terms of its expected clinical performance, including a discussion of any safety factors.

5.1 Preclinical Studies

5.1.1 Tensile Strength and Ultimate Elongation

Tensile strength and ultimate elongation represent the largest sustainable stress and stretching deformation on a test specimen before rupture occurs, respectively. The testing should be performed on material specimens taken from the thinnest location of the prosthesis shell. TPP suggests following the methodology described in ASTM D412 ("Vulcanized Rubber and Thermoplastic Rubbers and Thermoplastic Elastomers – Tension").

If tensile and elongation testing cannot be performed on the thinnest samples due to “curling”, an alternate test should be performed to ensure that this area is not the site of device failure under the type of stress conditions expected for the device.

5.1.2 Tear Resistance

Tear resistance is a measure of the capability of the implant against propagation of a puncture or small tear. The testing should be performed on material specimens taken from the thinnest location of the prosthesis shell. TPP suggests following the methodology described in ASTM D624 ("Tear Strength of Conventional Vulcanized Rubber and Thermoplastic Elastomers").

If the testing cannot be performed on the thinnest samples due to "curling", an alternate test should be performed to ensure that this area is not the site of device failure under the type of stress conditions being measured.

5.1.3 Integrity of Fused or Adhered Joints

Failure of a fused or adhered joint represents a potential source of leakage of the filler from the device. This testing provides a measure of the resistance of the device to such failures. If possible , each type of patch/shell joint and valve/shell joint should be tested. TPP suggests following the methodology described in ASTM F703. However, unlike ASTM F703, destructive testing should be conducted (i.e. test samples to failure). The force at failure should be reported.

For some button or domed shaped valves this testing may not be possible. In these cases valve competency testing can generally be related to clinical effectiveness and will substitute to ensure preclinical safety.

5.1.4 Abrasion

A sponsor may choose to develop a specific test to address only wear/abrasion and particulate generation. If the sponsor chooses to do so, then a complete description of the testing method with an adequate rationale should be provided. One suggested specific method of addressing wear/abrasion is as follows. Shell samples are taken from the top of the finished, sterilized devices and loaded with a 1000g mass. An abrading surface of silicone elastomer should be considered because it is more reflective of the in vivo situation.

If a sponsor chooses to use a different abrading surface because it is not possible to obtain particulate matter using a silicone elastomer surface, then a rationale for the abrading surface chosen should be provided. TPP suggests a mildly abrasive surface be used. In order to better simulate in vivo conditions and to adequately collect particulate matter, the testing should be conducted with the samples immersed in deionized water. The test should be conducted to determine the maximum number of cycles to failure. While failure may be defined as a tear, a sponsor should consider defining failure as a percentage reduction in implant thickness in order to prevent potential ruin of the abrading wheel. After every 10,000 cycles, the abraded particles should be removed and collected and the abraded area of the specimen examined.

The testing is stopped after failure or after the established number of cycles has been reached. The quantity and particle size distribution of the abraded material should be provided, with particular focus on the percentage of particles less than 100 micrometers, including photomicrographic documentation of the particles present in the debris field.

5.1.5 Static Rupture Testing of Total Device

A compressive force to the breast implant may be applied during daily activities, as well as during mammography or sleeping on the chest. Static rupture testing should be performed to capture the compressive static force required to rupture a total finished, sterilized device. The static loads as

well as the mode and location of failure should be reported.

5.1.6 Fatigue Rupture Testing of Total Device

Most materials are subject to a finite fatigue life when repeatedly stressed or flexed. Repeated compression, folding, bending, or flexing of the device will, with time, weaken the material of the shell and eventually lead to shell failure. These failure mechanisms are addressed by compressive fatigue testing in which a constant compressive force is cyclically applied to an intact breast implant until the device ruptures.

Fatigue testing of breast implants should only be done using load control tests. The samples should be cyclically loaded in compression to runout (X million number of cycles) and to determine failure at varying loads to generate an applied force versus number of cycles (AF/N) curve. The runout value should be based on expected *in vivo* cycles subjected to the implant in its lifetime. Adequate rationale for the runout value should be provided. An adequate number of samples should be tested to construct the curve, including the "elbow point", i.e. the location of the maximum change in curvature of the plot. The load at runout, with no failure, should be determined, as well as the mode and location of failure.

Results should be presented to include stress as the independent variable not just force. Stress allows for the comparison of fatigue results from different device sizes because the applied force is normalized for rupture site thickness and the increase or decrease in device size.

5.1.7 Static Impact Testing of Total Device

Static impact testing should be designed to address a range of worst case trauma to the breast implant, such as in car accidents. No standard methodology exists regarding impact testing, so the sponsor should provide a test method along with adequate rationale.

The test set-up should involve a range of weighted strikers and drop heights to simulate the range of worst case trauma. The contact area of the striker, the range of weights, the drop height, and speed should be justified. The impact energy, determined from the total area under a generated stress-strain curve, should be provided, as well as the mode and location of failure.

5.1.8 Valve Competence

This testing pertains to saline-filled implants with valves, as well as any alternative breast implants with valves. Valve competence tests conducted on saline-filled breast prostheses should demonstrate the resealing capabilities of the valve. The devices can be subjected to hydrostatic forces that tend to force fluid out of the device, causing a deflation and change in size and shape. The most likely source for increased pressure inside the devices would be from patients reclining with various body elements (head, arm, trunk, etc.) pressing on their prostheses. The maximum expected pressures exerted on the device during typical service loading should be defined, and the devices should be tested in a pressure regime that allows for a margin of safety.

TPP suggests the methodology described in ASTM F703. ASTM F703 states that there shall be no leakage observable for five minutes after a normally closed valve is subjected to a retrograde pressure equivalent to 30cm H_2O and then to a retrograde pressure equivalent to 3cm H_2O. However, TPP does not believe that ASTM F703 tests the efficacy of the device under actual *in vivo* load conditions. Therefore, the sponsor should predefine a pressure that adequately defines *in vivo* conditions, with a rationale, and provide testing at that pressure.

Thus, sponsors should demonstrate that valve integrity is maintained at actual anticipated maximum *in vivo* loads, well in excess of those stipulated by the F703 standard. To accomplish this, the devices should be gradually loaded until valve failure occurs and a maximum service pressure can be defined for the device. Whether the failed test valves reseal upon removal of the excess failure-inducing pressures should also be reported.

In addition, valve integrity testing should be performed on devices that were used in the fatigue testing described in section 5.1.7 above. This will provide data on the performance of the valve after simulated use. Pressure at failure of the fatigue-subjected samples can then be compared to those that were not subjected to prior fatigue loads.

5.1.9 Cohesivity of Silicone Gel or Alternative Filler

This testing pertains to silicone gel-filled and alternative filler implants. Cohesivity testing should be performed to measure both the rheological (flow) properties and the integrity (connectivity) of the gel. Testing should be conducted on gel-fill material obtained from finished, sterilized devices.

Two suggested methods are briefly described in ASTM F703. However, because the methods are not completely described, the sponsor should provide a complete description of the test method used, including the pass-fail criteria, with an adequate rationale. The results reported should be appropriate for the testing methodology (e.g., length of pendant gel, level of gel slump, etc.).

5.1.10 Biocompatability Studies

Biocompatability testing of all materials that can potentially come in contact with the body is required in order to ensure compliance with Sections 11 and 15 of the Medical Devices Regulations.
Biocompatability or biological testing is done following the toxicological risk assessment required by EN 1441 (Medical Devices - Risk Analysis) or ISO/DIS 14971 (Medical Devices - Risk Management, Part 1: Application of Risk Analysis). The general principles applied to the biological evaluation of materials and devices are described in ISO 10993-1:1997 (Biological evaluation of medical devices - Part 1: Evaluation and Testing).

These tests differ from basic toxicity tests, in that they attempt to mimic the conditions of clinical exposure and thus may provide an indication of the probability of adverse effects arising during use. It may not be necessary to perform all tests suggested by the standard, where the proposed materials have been previously studied or used extensively.

5.2 Clinical Studies

Studies may include separate patient cohorts of primary augmentation, primary reconstruction, and/or revision. Since these studies are complicated by the fact that some patients receive implants for different reasons (e.g., a woman may receive one implant for reconstruction and one for augmentation), data should be recorded and analyzed on both a per patient and per device basis. The patient/device is classified by her indication upon entry into the study.

The following should be considered when classifying a patient/device. If a reconstruction patient undergoes contralateral augmentation, that *patient* is classified as reconstruction. The device classifications are both reconstruction. If a revision patient (i.e. the patient entered the study due to replacement of an existing implant, irregardless of the type/manufacturer of the original implant), undergoes contralateral augmentation, that *patient* is classified as a revision patient. The patient population can be further subdivided into a revision reconstruction or a revision augmentation. The device classification is one revision and one augmentation. If a revision (removal with replacement) occurs during the study (i.e. after initial implantation), the *patient/device* is classified based on the indication at original implantation upon entry into the study.

If patients who undergo removal and replacement with the same manufacturer's implant, then continued follow-up is expected. For patients who undergo removal without replacement or removal with replacement with another manufacturer's implant, then the TPP still encourages sponsors to continue follow-up evaluations.

Full patient accounting and adequate and appropriate safety and effectiveness data presentations are essential.

5.2.1 Study Design / Statistical Issues

A complete description of the protocol should be provided. This includes explanations of the study objectives, descriptions of primary and ancillary hypotheses, definitions of the study population (i.e. inclusion and exclusion criteria), methods of randomization (if used), number and locations of investigational sites, enrollment procedures, descriptions of surgical techniques, and lists of allowable ancillary interventions and/or drugs (e.g., use of closed capsulotomy, use of intraluminal corticosteroids or antibiotics). In addition, an explanation of how the control group, was selected. Alternately, if no control group was used adequate justification must be provided.

All hypotheses to be tested, both null and alternative, should be clearly stated. For safety, this includes the hypothesized rates of grade III/IV capsular contracture, explantation (for any reason), infection, and rupture. Hypothesized rates of effectiveness benefits (i.e. improvement in body esteem scale) may also be included. Appropriate statistical techniques should be defined prospectively and employed to test these hypotheses and support claims of safety and effectiveness.

Adequate demonstration that the patients in the study are representative of the population for whom the device is intended (i.e. with respect to patient age and indication for use) should be provided. This may be based on detailed patient demographic analyses and characterizations of patient baseline characteristics.

Statistical rationale that the sample size is adequate to provide accurate measures of the safety and effectiveness of the device should be provided. This includes, at a minimum, identification of effect criteria (clinically significant difference in the response variables to be detected), desired precision for rate estimates, statistical error tolerances of alpha and beta, anticipated variances of response variables (if known), any assumptions or statistical formulas with copies of references used, reasonable estimations of lost-to-follow-up rates, and all calculations used. Sample size estimates should be based on the precision of safety and effectiveness outcomes or detecting a clinically meaningful difference at two years but with consideration to lost-to follow-up rates estimated for 10 years of patient follow-up. If sample size estimates are based on the precision with which complication rates can be estimated, then the sample size should be large enough to ensure that this precision is within a pre-specified number of percentage points which TPP would consider acceptable, based on 95% confidence intervals.

For example, for sufficient numbers of patients of women with primary augmentation or primary reconstruction (i.e. 75% primary augmentation and 25% primary reconstruction) to determine the rupture rate with reasonable precision, 500 women will be needed to be followed at by the end of the study (i.e. 10 years post-implantation). The pool of reconstructive patients will necessarily not include breast cancer survivors, in order to achieve follow requirements.

Estimating a 40% drop out rate at 10 years, recruitment of at least 850 patients would be required. This will provide a worst case precision of +/-4% at a rupture rate of 50%, and this precision will improve as the rate moves away from 50%, with a +/-1.9% precision at a rupture rate of 5% or 95%. Sample size may also be justified based on survival analyses, using the method of Peto, which would result in a worst-case precision of +/-3%, given the same sample size and dropout rate (Peto, Richard, et al., Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and Examples. British J. Cancer 35:1-39, 1997.). Since both safety and effectiveness data from patients presenting for revision of an existing implant may be significantly different from that of primary implantation patients, a proportion of patients presenting for revision should be included. Estimating that approximately 20% of patients present for breast implants due to revision, the final sample size should be increased by 20% (i.e. approximately 1,000 total patients enrolled) to accommodate recruitment of approximately 150 revision patients.

Statistical rationale for pooling across the following confounding variables should be provided: patient age; investigational site; device type (i.e. single lumen vs. multi-lumen); device size; device surface texture (i.e. smooth vs. textured); valve type (e.g., diaphragm vs. leaf, etc.); device placement (i.e. subglandular vs. retromuscular); surgeon experience and technique (if applicable);

and timing of reconstruction (i.e. immediate vs. delayed).

All relevant variables should be reported for each subpopulation of patients in order to evaluate the risk/benefit ratio. For each relevant subgroup, a sufficient number of patients should be followed for a sufficient length of time to adequately support all claims (explicit and implied) in any licence application. Patient subgroups include primary (initial) augmentation, primary reconstruction without prior tissue expander, primary reconstruction with prior tissue expander, and revision (either due to cosmetic, medical, or surgical reason(s) and following either initial augmentation or reconstruction).

Additional analyses for the degree of device safety and effectiveness are recommended for the following variables: patient age, indication for use (i.e. augmentation vs. reconstruction vs. revision), etiology and duration of breast abnormality (if applicable), device type (i.e. single vs. multi-lumen), device style, valve type (e.g., leaf, diaphragm, etc.), device surface type (i.e. smooth vs. textured), surgical incision site, device placement (e.g., retromuscular, subglandular), investigational site, surgeon experience and technique, type of reconstruction (i.e. immediate vs. delayed), use and type of surgical pocket irrigation, and use and type of intraluminal agents (if used). Statistical analyses with logistic regression or Cox regression analysis is suggested to determine which of these variables are associated with each safety and/or effectiveness outcome. Some subgroup analyses may also be necessary.

5.2.2 Safety Assessment

Rates and time course evaluations for the following should be provided, regardless of the relation of the device to the event. For the time course presentations, survival analyses are recommended.

The following should be documented: the incidence and reason(s) of revisions/explantations (for either cosmetic, medical, or surgical reasons); the frequency, reason(s), and severity of additional surgical procedures, (including but not limited to incision and/or drainage of abscess/hematoma/seroma, excision of masses/tissues/calcifications, capsulotomy - both open and closed - capsulectomy, etc.); the incidence, reason(s) and consequences of device failures (including rupture, leakage, extensive silicone gel or alternative filler material bleed); the incidence, severity, duration of, and the method of resolution of all other complications (including but not limited to Baker Grade of fibrous capsular contracture, infection, calcification, migration, extrusion, skin erosion, necrosis, lymphadenopathy, delayed wound healing, breast/chest/axillary mass(es) formation, iatrogenic injury, hematoma, pain, and seroma); the incidence, severity, and consequences of cosmetic complications (e.g., distortion, wrinkling, scar formation, visibility of the implant, asymmetry); the incidence, timing of, and severity of alterations in nipple or breast sensation; the incidence, timing of, and severity of interference and/or difficulties with lactation; the incidence and nature of difficulties with pregnancy or resulting offspring; the incidence and nature of mammographic detection difficulties; the incidence and nature of mammographic changes; the incidence and cause of patient deaths (i.e. from post-mortem examinations); the incidence and reason(s) of patient dissatisfaction due to implant complications and removal(s); and any other

device malfunction or adverse health event (including any effects on the immune system and the reproductive system).

For silicone gel-filled prostheses, the characterization of the time course evaluations, incidence, and clinical consequences of silent rupture should be provided. Silent rupture is defined as a loss in the integrity of the shell, regardless of whether or not the silicone gel material has been demonstrated to have migrated from the shell. The incidence, timing, and clinical consequences should be determined via prospective, sequential screening of a subgroup of the study population utilizing diagnostic radiographic or other techniques of adequate sensitivity and specificity. For standard silicone gel-filled prostheses, magnetic resonance imaging (MRI) is recommended as the current method of choice for detecting this event. Sequential screening of a subgroup of patients undergoing MRI to detect silent rupture should be carried out at 6 months, 2 years, 5 years and 10 years. Any MRI studies should utilize the following terms to describe or define the results of these studies.

> **Intracapsular Implant Rupture (Silent Rupture)**: is defined as rupture of the implant shell (elastomer envelope) allowing the release of silicone gel, which does not extend beyond the intact fibrous capsule.
> **Extracapsular Implant Rupture**: is defined as rupture of both implant shell and the fibrous capsule with silicone leakage extending into surrounding tissues.
> **Uncollapsed Implant Rupture**: is when a ruptured implant shell does not collapse or only partially collapses. The linguine sign will not be present. The reasons why some ruptured implants do not completely collapse is unclear. One theory is that older implant shells are thicker and have fixation patches, making collapse less likely.
> **Silicone Gel Bleed**: Gel bleed occurs in all silicone implants. This does not constitute rupture.

Details of MRI techniques and of the equipment used must be provided with the results.

Breast implants are known to alter the appearance and quality of radiographs produced by conventional mammography. For an individual patient undergoing routine screening mammography, the sponsor should collect the incidence and extent of tissue fibrosis and calcification around the prosthesis and their impact on the correct and timely detection of breast tumors by mammography.

Despite the large body of information published regarding breast implants and the development of rheumatic or connective tissue diseases (CTD), the association between breast implants and CTD remains unresolved. While recent reviews [1.2.3] have provided some evidence that breast implants are not associated with a large increase (i.e. relative risk greater than 2) in defined CTD, these data are limited in that they are not prospective (resulting in potential under reporting due to recall bias), do not address incomplete symtomatology for definitive diagnosis, lack consistent evaluations and follow-up, lack adequate duration of follow-up, and report pooled data from a

variety of implant compositions rather than from product specific compositions. Furthermore, in general, the population for which breast implants is indicated, particularly the augmentation cohort (i.e. females in the reproductive age group), is inherently at greater risk for developing CTD than the older population. Therefore, TPP believes that the sponsor may be able to provide valuable research information regarding this issue and, therefore, suggests that sponsors collect CTD data in a prospective manner for a sufficient duration of follow-up. The sponsor may also be able to provide valuable research information by characterizing the incidence and time course presentations for the development of rheumatic diseases (including but not limited to rheumatoid arthritis, systemic lupus erythematosus, discoid lupus, scleroderma, vasculitis, polymyositis, dermatomyositis), rheumatic syndromes (including Raynaud's phenomenon, Sjogren's syndrome, CREST, morphea, carpal tunnel syndrome, multiple sclerosis-like syndrome, multiple myeloma-like syndrome, chronic fatigue syndrome, and fibromyalgia), rheumatic signs and symptoms (such as hair loss, facial rash, photosensitivity, dry eyes, dry mouth, arthralgias, myalgia, difficulty swallowing, morning stiffness >30 min, ocular inflammation/retinitis/optic neuritis, muscle weakness, joint swelling for >6 weeks, pleurisy, skin rash, and lymphadenopathy), and other reported signs/symptoms (such as cognitive dysfunction, fatigue, paresthesia, dizziness, abnormal bruising or bleeding, purpura, unexplained fever, urticaria, telangiectasia, and petechiae). This evaluation should be conducted on all patients yearly, with follow-up by a rheumatologist or other appropriate specialist, if indicated, and with collection of serological information (e.g., ANA, RF, ESR, immunoglobulin levels, CPK, SPEP, complement levels, etc.) if indicated.

Epidemiologic studies do not indicate that there is a large increased risk for connective tissue disease overall in women with breast implants.[1,2,3] Laboratory studies have shown that certain autoantibodies (e.g., to collagen or anti-nuclear antibodies) are present in some women with breast prostheses, but there is no evidence that they are harmful. Tests for anti-silicone antibodies also have been reported, but have not been validated. It is unclear what the tests measure and if the results are clinically meaningful. Similarly the clinical relevance of measuring anti-polymer antibodies in women with silicone breast implants has not been established. Available blood tests have not been shown to provide useful diagnostic information, so no specific tests are currently recommended.

Patients should be monitored periodically and regularly for the occurrence of all complications and adverse events for a minimum of 10 years post-implantation (see section 5.2.1 for a detailed description on sample size assessment). Follow-up frequencies are suggested as, at a minimum, of 3, 6, 12, 18, and 24 months, and then, at minimum, annually thereafter. Annual visits after the 2-year time point are recommended due to retention of postal address changes of one year and to minimizing lost-to-follow-up. The purpose of these visits/contacts is to assess for the incidence, severity, duration of, and method of resolution of pain; masses; rupture/leakage; explantation with or without replacement for either cosmetic, medical, or surgical reasons; grade III/IV capsular contracture; the presence and consequences of additional surgical procedures (including but not limited to capsulotomy --both open and closed -- capsulectomy; incision and/or drainage of

abscess, hematoma, seroma; and, removal of masses, tissues, calcifications); cosmetic complications (i.e. wrinkling, distortion, visibility of the implant, asymmetry); lactation difficulties; pregnancy complications; mammographic changes and/or difficulties; radiographic assessment for silent rupture (gel-filled and possibly alternative-filled); active CTD follow-up.

5.2.3 Effectiveness Assessment

All marketing claims (both explicit and implied) of equivalence or superiority to existing implants or therapies should be supported with statistically justified numbers of patients, clinically relevant endpoints, and with direct comparisons made to an appropriate control group.

The anatomical effect of the implant should be assessed. This may be evaluated by comparing matched analyses of before and after bra and cup sizes, symmetry, and/or other standardized measurements.

The quality of life (QOL) benefits should be evaluated using valid and reliable instruments to assess the quality of life impact of the device. Currently, there are no QOL instruments which have been developed and validated in a breast implant population which capture all of the important QOL domains (i.e. physical, social, emotional) as well as the positive and negative aspects of implantation on breast implant recipients. In order to make claims of improvement in health related quality of life, sponsors should develop and validate such QOL measures for their products in a breast implant population. However, at minimum, the following QOL assessments should be included in breast implant studies as secondary endpoints of effectiveness: a measure of self esteem (i.e. Rosenberg Self Esteem scale), a measure of body image (i.e. Body Image Scale), and a measure of general health related quality of life (i.e. SF-36). These assessments should be prospectively collected for presurgical and postsurgical repeated measures. Sponsors should describe the timing of administration of QOL instruments with respect to delayed versus immediate reconstruction in reconstruction patient. Stratification of the data according to indication (i.e. augmentation, reconstruction, and revision) as well as correlation of the QOL data with other clinical outcomes and other control/comparison groups is recommended. The minimum duration of these assessments should be sufficient to capture stabilization of these parameters. A minimum duration of 2 years is recommended.

It is recommended that a measure of global patient satisfaction be assessed. This assessment should incorporate the effects of the following: the initial surgical procedure, adjunctive surgical and medical procedures, complications, and whether the expected benefits of the procedure and of the implants have been met. Patient satisfaction data assessing the effects of device explantation, regardless of whether the device was replaced, also is suggested.

5.3 Process Validation Studies

Standard operating procedures for sterilizing and qualifying the sterilization process must be provided. Provided information should include the method of sterilization; the detailed sterilization validation protocol/results; the sterility assurance level; the type of packaging; the

packaging validation protocol/results; residual levels of ethylene oxide, ethylene glycol, and ethylene chlorohydrin remaining on the device after the sterilization quarantine period, if applicable; and the radiation dose, if applicable.

6.0 Device Label

6.1 Package Insert

The package insert used for a breast implant is typically a combination package insert / surgical technique manual. The sponsor may choose to provide this information in separate pieces of labeling. Otherwise, the information should include, but is not limited to, the following: device name; brief device description with material information; indications for use; list of any pertinent contraindications, warnings, precautions, and adverse events; sterile notation; a description of any pre-implant training necessary for the surgical team; a description of how to prepare the patient (e.g., prophylactic antibiotics), operating room (e.g., what supplies should be on hand), and implant for device implantation; instructions for implantation, including surgical approach and device specific information (depends on type of breast implant); intraoperative test procedures to ensure implant integrity and proper placement; instructions for follow-up, including whether patient antibiotic prophylaxis is recommended during the post-implant period and during any subsequent dental or other surgical procedures; and how to evaluate, and how often to evaluate, implant integrity and placement.

The directions should instruct caregivers to specifically question patients prior to surgery for any history of allergic reaction to any of the device materials or filling agents. Troubleshooting procedures should be completely described. The directions for use should incorporate the clinical experience with the implant and should be consistent with those provided in other sponsor-provided labeling.

Implant failure is a critical assessment. Therefore, sponsors should advise against closed capsulotomy because it has been shown to potentially result in implant rupture. Additionally, sponsors should advise against the addition of substances into the filler (i.e. betadine, steroids, and antibiotics) other than those recommended because the substance may potentiate and/or accelerate delamination of the shell.

6.2 Patient Labeling

Patient labeling should include the information needed to give prospective patients realistic expectations of the benefits and risks of device implantation. Such information should be written and formatted so as to be easily read and understood by most patients and should be provided to patients prior to scheduling implantation so that each patient has sufficient time to review the information and discuss it with her physician(s). Technical terms should be kept to a minimum and should be defined if they should be used. Patient information labeling should not exceed the seventh grade reading comprehension level.

The patient labeling should include, at minimum, the following information: indications for use;

relevant contraindications, warnings, and precautions; potential complications, including the possible methods of resolution; anticipated benefits and risks (to give patients realistic expectations of device performance); alternative treatments, including no treatment and the benefits and risks of each; advisement to talk with her doctor about the alternative treatments and which might be right for her; what to expect after surgery, including length of recovery; symptoms to tell her doctor about immediately; whom to contact if questions arise; activities that could damage or rupture the implant; why the implant is not a "lifetime" implant; possible need for device modification, removal, and/or replacement; and clinically supported information, if available, on the lifetime of the implant, including the possible need for modification, removal, and/or replacement.

7.0 Special Considerations

The following should be reviewed by the physician with the patient at least a few days prior to surgery: the package insert for the device she is to have implanted; any specific patient labeling information; the Informed Consent, which must be signed prior to surgery; and any additional information related to the device such as lifetime replacement and reimbursement policy information.

At the time of surgery, the physician should complete an identification card for the patient that provides specific device information (e.g., lot number).

The stage and status of breast cancer can impact on future development of cancer. Furthermore, the presence of chemotherapy, radiation, or other cancer treatments can impact the development of local complications with implants. These issues may impact the evaluation of the safety and effectiveness of the device. Therefore, these data should be collected on all reconstruction patients and on augmentation/reconstruction patients who develop breast cancer during the course of the study.

8.0 References

1) Silicone Gel Breast Implants, report of the Independent Review Group, July 1998.

2) Silicone Breast Implants in Relation to Connective Tissue Diseases and Immunological Dysfunction, submitted to the United States District Court (Northern District of Alabama), November 30, 1998.

3) The Safety of Silicone Breast Implants, Institute of Medicine, National Academy of Science, June 22, 1999.