



**SUMMARY BASIS OF DECISION (SBD)
INAMED STYLE 410 SILICONE-FILLED BREAST
IMPLANTS**

Inamed Corporation

Application No. 88573

Licence No. 72262

Date Issued	2006/10/20
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Health Products and Food Branch

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Health Products and Food Branch

Également disponible en français sous le titre: Sommaire des motifs de décision (SMD), INAMED STYLE 410 SILICONE-FILLED BREAST IMPLANTS, Inamed Corporation, N° de la demande 88573, N° de l'homologation 72262.

FOREWORD

Health Canada's Summary Basis of Decision (SBD) documents outline the scientific and regulatory considerations that factor into Health Canada regulatory decisions related to drugs and medical devices. SBDs are written in technical language for stakeholders interested in product-specific Health Canada decisions, and are a direct reflection of observations detailed within reviewer reports. As such, SBDs are intended to complement and not duplicate information provided within the Operator's Manual.

Readers are encouraged to consult the 'Reader's Guide to the Summary Basis of Decision - Medical Devices' to assist with interpretation of terms and acronyms referred to herein. In addition, a brief overview of the medical device application review process is provided in the Fact Sheet entitled 'Safe Medical Devices in Canada'. This Fact Sheet describes the factors considered by Health Canada during the review and authorization process of a device licence application. Readers should also consult the 'Summary Basis of Decision Initiative - Frequently Asked Questions' document. These documents are all available on the Health Canada website.

The SBD reflects the information available to Health Canada regulators at the time a decision has been rendered. Subsequent applications reviewed for additional uses will not be captured under Phase I of the SBD implementation strategy. For up-to-date information on a particular product, readers should refer to the most recent Operator's Manual for a product. For information related to post-market warnings or advisories as a result of adverse events, interested parties are advised to access the Health Canada website.

For further information on a particular product, readers may also access websites of other regulatory jurisdictions, available under 'Related Links' on the Health Canada website. The information received in support of a Canadian device licence application may not be identical to that received by other jurisdictions.

Other Policies and Guidance:

Readers should consult the Health Canada website for other medical device policies and guidance documents. In particular, readers may wish to refer to the 'Management of Applications for Medical Device Licences and Investigational Testing Authorizations Policy'.

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1 DEVICE AND APPLICATION INFORMATION

Device Name	Inamed Style 410 Silicone-Filled Breast Implants
Manufacturer	Inamed Corporation
Medical Device Group	Musculoskeletal
Biological Material	N/A
Combination Product	Yes [] No [X]
Drug Material	N/A
Application Type and No.	Application for a new medical device licence, No. 88573.
Date Licence Issued	2006/10/20
Device Catalogue/Model No.	Refer to http://www.mdall.ca/
Licence No.	72262
Intended Use	<p>The device is intended for reconstruction of the breast following a mastectomy or for breast augmentation. Breast augmentation is indicated for women at least 22 years old. Breast augmentation includes primary breast augmentation to increase the breast size, as well as revision surgery to correct or improve the result of an original primary breast augmentation surgery. Breast reconstruction includes primary reconstruction to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. Breast reconstruction also includes revision surgery to correct or improve the result of an original primary breast reconstruction surgery.</p> <p>The device is contraindicated for: women with infection anywhere in their body, women with existing cancer or pre-cancer of their breast who have not received adequate treatment for those conditions, and women who are currently pregnant or nursing.</p>

2 NOTICE OF DECISION

On October 20 2006, Health Canada issued a Class IV Licence with conditions to Inamed Corporation for Inamed Style 410 Silicone-Filled Breast Implants. Licence issuance was subject to five conditions encompassing annual follow-up data updates to Health Canada and further measures to ensure the safe use of these devices sold in Canada.

A silicone gel-filled breast implant is a sac (implant shell) of silicone “rubber” (elastomer) filled with silicone gel. It is surgically implanted either under (and within) the breast tissue or under the chest muscle.

Breast implants are indicated for reconstruction of the breast following a mastectomy or for breast augmentation. Breast augmentation is indicated for women at least 22 years old. Breast augmentation includes primary breast augmentation to increase the breast size, as well as revision surgery to correct or improve the result of an original primary breast augmentation surgery. Breast reconstruction includes primary reconstruction to replace breast tissue that has been removed due to cancer or trauma or that has failed to develop properly due to a severe breast abnormality. Breast reconstruction also includes revision to correct or improve the result of an original primary breast reconstruction surgery.

Breast implant surgery is contraindicated in women with infection anywhere in their body, women with existing cancer or pre-cancer of their breast who have not received adequate treatment for those conditions, and women who are currently pregnant or nursing.

The application included: a quality plan, material specifications, chemical extraction analysis of materials, manufacturing details, process validation information, sterilization data, packaging and shelf life data, mechanical testing, gel-bleed testing and toxicological analysis, biocompatibility studies, prospective clinical data, explant retrieval studies, literature studies, labelling information, and post-marketing plans and projections for large scale long-term clinical trials.

The market authorization was based on the quality of information presented and a demonstration of serious commitment to follow the current prospective clinical trial through to ten years in accordance with the study protocol. Complete clinical study data was provided through three years post-implantation. Most complications were resolved by the three-year follow up, the majority of which were resolved with non-surgical treatment or no treatment at all. The long-term safety and effectiveness of these implants have not yet been established, however as a condition of licensing, Inamed is required to follow-up their Core Study of 1000 patients through to ten years and to commence a large-scale post-approval study designed to measure potential rare adverse events over the long term. An external review of the application by an Expert Advisory Panel (EAP) included input from the patient and

scientific communities, as well as other interested members of the public. This consultation resulted in a series of recommendations (EAP Report, November 2005) which were also taken into account during the application review. Inamed Style 410 Silicone-Filled Breast Implants should be used under the conditions stated in the labelling, taking into consideration the potential risks associated with the use of this device.

Detailed conditions for the use of Inamed Style 410 Silicone-Filled Breast Implants are described in the Directions for Use section of the Package Insert. Based on the Health Canada review of data on quality, safety, and effectiveness, it is considered that the benefit/risk profile of Inamed Style 410 Silicone-Filled Breast Implants is acceptable.

3 SCIENTIFIC AND REGULATORY BASIS FOR DECISION

3.1 Introduction

The Inamed Style 410 Silicone-Filled Breast Implants are silicone gel-filled implantable devices intended to augment or reconstruct the female breast. There are twelve models in the Style 410 Matrix, relative to projection and height. To date no major complications have been reported with the use of these implants.

At the time of review the Style 410 devices were available under Health Canada's Special Access Programme (SAP). One adverse event (wound dehiscence) associated with implantation with a Style 410 device has been reported to date. Inamed has filed a Pre-Market Authorization (PMA) for this product with the US Food and Drug Administration (FDA) which is currently under review. This device is currently sold openly as a Class III device in the European Union.

Inamed provided customer complaint data reported for the Style 410 family from May 1993 to April 2006. All Style 410 products share identical materials and processes and only differ in shape. Complaints related to implantation of the device as well as complaints related to implant appearance, packaging/labelling and other pre-implant events were provided. Post-surgical incidents were less than 0.2% overall and included capsular contracture, infection, and implant displacement.

3.2 Device-Specific Detailed Information

The Style 410 silicone gel-filled breast implants are identical to Inamed's other silicone gel-filled styles in terms of the shell materials, patch formation, and processing.

These implants are manufactured by the same texture process as Inamed's round silicone gel-filled breast implants with the BIOCELL[®] surfaces (Application No. 60524 and 61865). The resulting open pore structure consists of pore diameters from 100-600 µm (usually 300 µm) and pore heights from 200-350 µm. The chemical composition of the textured surface layer is identical to the base layers of the shell. The shell thickness range is 0.018"-0.060".

The Inamed Style 410 implants are made from the same platinum-catalyzed polysiloxane gel as their round silicone gel-filled implants but in a more cohesive or cross-linked form. The Style 410 implants are also anatomically shaped. There are twelve implant models based on low, moderate, and full height; and low, moderate, full, and extra full projection to form what Inamed calls the "Biodimensional System". Sizes vary from 100-775 g.

Another feature of the cohesive gel implants are the orientation markings on the posterior and anterior surface of the shell. The orientation marks form slight projections on the implant surface and are designed to assist the surgeon in the correct placement of the device within the surgical pocket.

3.3 Devices Containing Biological Material

The Inamed Style 410 Silicone-Filled Breast Implants do not contain any biological material.

3.4 Safety and Effectiveness

3.4.1 List of Standards

A complete list of standards was provided in the application and is considered to meet the requirements of the Canadian *Medical Devices Regulations*. There is no recognized list of standards for breast implants; standards adhered to in this application included the following:

ASTM D 412-98	Standard Test Methods for Vulcanized Rubber and Thermoplastic Elastomers - Tension
ASTM F 703-96	Standard Specification for Implantable Breast Prostheses
ISO 10993	Biological Evaluation of Medical Devices

3.4.2 Method of Sterilization

The Style 410 implants are dry heat sterilized and validated by exposure to 10^{-6} organisms of *Bacillus subtilis*, *Candida albicans*, and *Aspergillus niger*. Shelf-life has been validated for five years; the devices are not to be resterilized.

3.4.3 Manufacturing and Quality Control

Manufacturing Process

Each of the silicone gel-filled breast implants are manufactured by dipping a mandrel into a dispersion of silicone. The shell is built in multiple dipping steps and is composed of three distinct layers. The middle layer is designed as a barrier to the diffusion of low molecular weight silicones, and is referred to as the barrier layer. These layers form the barrier shells common to both smooth and textured silicone gel-filled breast implants manufactured by Inamed.

A complete list of raw materials used in the device was provided along with the specific role and location in the final product. Material data sheets were also supplied for each component, including acceptance criteria and description of polymeric components.

Methods used in, and the facilities and controls used for, the manufacture, processing, packaging, and storage of the device were reviewed and found to be satisfactory.

Process Validation Studies

Results of all process validation studies along with procedures for monitoring and controlling the validated process were submitted and found to be satisfactory.

Quality Plan

The quality plan was reviewed and found acceptable.

Quality System Certificate

A quality system certificate (ISO standard 13485) that has been issued by Canadian Medical Devices Conformity Assessment System (CMDCAS) recognized registrars has been provided.

3.4.4 Preclinical Studies

Chemical Tests

Chemical analysis was performed on the elastomer shell (including patch) and the filler material. Molecular weights and polydispersities of the polymers in the elastomers of the device shell layers and peroxide patch elastomer were determined by GPC against polystyrene standards.

In addition, a study was conducted to verify that the post-cure manufacturing process of the peroxide catalyzed patch layer sheeting effectively removes residual byproduct such as benzoic acids, resulting from catalyst decomposition during vulcanization and post-cure. Polychlorinated biphenyls (PCBs) were of specific public health concern due to their known toxicity. The analysis identified only dichlorobenzoic acids present in the material prior to and following post-cure processing (at a level of 69 mg/kg). This chemical was not a toxicological concern at the low concentration reported, nor is it cited in any listing or databank as a potentially carcinogenic chemical. Other carbonyl compounds, polychlorinated biphenyls, and tetrachlorobiphenyls were not detected at the PQL's (Practical Quantitation Limits) listed in the report.

Gel filled implant materials containing platinum and tin were also analyzed for residuals of these metals. During manufacture, platinum is added to the gel, elastomers used for the shell, barrier layer, and patch in order to catalyze the curing reaction. Tin is present in the gel, shell, and patch as a result of its presence at trace levels in the materials used to synthesize the elastomers used for these components. The results of the analysis provided are consistent with the reference, and the concentration of platinum by weight of the implant material in shells, gel, and patch material is in the range of 2-4 ppm. The concentration of the tin in implant shells and gel is below 1 ppm and the concentration of the tin in the patch varies due to the difference in materials used in patch construction.

It has been established that the residual form of platinum used to manufacture silicone gel-filled breast implants is not potentially toxic. This has been recently supported by a US-FDA *Backgrounder on Platinum in Silicone Breast Implants* issued on June 16, 2006 and in two articles in the peer-reviewed scientific journal, *Analytical Chemistry* (August, 2006). These publications discuss the evidence that the residual form of platinum is in the zero oxidation state, which does not pose a health risk to women with breast implants.

A trace metals assay was also conducted on other metals in the silicone materials via atomic absorption spectroscopy. Of the twenty-three elements analyzed, only six to seven elements were found in detectable limits of each material. Each detectable concentration was well within acceptable (certifiable) non-toxic levels of the maximum metals content.

Physical Tests

Since all the materials used in the cohesive gel implants are the same as those used in the standard gel implants, not all mechanical testing was reconducted. The following tests were conducted on the Style 410 implants:

- Static rupture
- Cyclic fatigue
- Static impact
- Cohesivity of silicone gel
- Gel bleed

Test results demonstrated that the performance of the Style 410 implants met the physical and mechanical design goals and is safe and acceptable for clinical use.

The EAP suggested that while the potential mechanisms of rupture have been adequately studied and that the data are sufficient to establish how the devices perform *in vivo*, the data do not address all aspects of long-term safety. As a condition of licensing, Inamed will be required to submit annual reports to update Health Canada of the ongoing follow-up of the 1000 Core Study patients through to ten years. This condition is considered to satisfy the advice of the EAP.

Biocompatibility Tests

Since all the materials used in the cohesive gel implants are the same as those used in the standard gel implants, some of the testing was previously performed and submitted with the application for the standard gel implants. The following testing has been provided to date:

- Radiolabelled pharmacokinetics
- Literature review on pharmacokinetics
- Cytotoxicity
- Implantation testing and histopathology
- Acute pyrogenicity
- Acute systemic toxicity and irritation
- Hemocompatibility
- Dermal sensitization
- Subchronic toxicity
- Reproductive/developmental toxicity
- Immunotoxicity
- Genetic toxicity
- Chronic toxicity and carcinogenicity

All testing demonstrated that the shell, gel, patch, and orientation components were non-toxic and biocompatible.

In Vivo Animal Tests

Results of the animal studies conducted in the biocompatibility assessment showed that the test articles were not mutagenic, sensitizers, or reproductive or developmental toxins.

In consideration of the advice provided by the EAP, Inamed was requested to submit a literature review on hypersensitivity and autoimmune reactions. This review covered the literature published between 1966 and January 2006 and was conducted by an independent scientific research firm.

Several studies have reported evidence of delayed-type hypersensitivity in animal models, suggesting that silicone may induce cell-mediated immunity. However, based on the consistent lack of association between autoimmune diseases and breast implants in humans and the absence of standardized animal models to conduct such testing, further animal testing is not justified at this time.

Gel Bleed (Diffusion) Studies

Gel bleed testing¹ was conducted in accordance with the standard method outlined in ASTM F703 using a standard silicone disk along with a millipore disk supported by octadecyl carbone (C₁₈) as the adsorbant. In this test, a silicone gel implant is placed on an adsorbant disk which is weighed at weekly intervals over an eight-week period. Testing was conducted on the Style 410 implants with a 3M millipore filter because the C₁₈ millipore disks better simulate the type of adsorption experienced in a lipid-like environment in the body than the silicone disks recommended in the standard ASTM method. However, the standard ASTM method is designed to test smooth implants to limit the variability in the shell texturing process, which is dependent on the implant manufacturer. Smooth implants provide a worst-case scenario in this test.

The lack of appreciable gel-bleed results in both versions of the test further supported the quantitative chemical analysis gathered using gas chromatography and flame ionization detection (GC-FID) which demonstrated low quantities of silicone species, particularly lower molecular weight species (<1500) in Inamed's Style 410 shell, patch, and gel.

¹ The term "gel bleed" is a well-known term in testing of gel-filled breast implants. However, the gel in its entirety is not what is tested but rather the silicone fluid or oil, which is a component of the silicone gel. The silicone fluid or oil is extracted from the implant shell in this test on silicone disks in accordance with the standard method (ASTM 703). The disks are pre-weighed and then re-weighed after different time periods to assess the quantity of silicone fluid release or "gel bleed".

Inamed also tested intact explanted Style 410 implants to determine the potential of weight loss as a function of time. Compared to the specified nominal weights of the device, the actual explanted device weights demonstrated no significant change in weight up to 8.5 years.

Retrieval Testing

A retrieval study report was provided for the Style 410 breast implants. The purpose of the study was to investigate the modes and causes of rupture (both intro-operative and *in vivo*) of returned Style 410 implants (US and international) manufactured after February 3, 1999. Devices included in the study were to be received in the laboratory before June 30, 2005. A total of 633 explant devices were provided. Laboratory analysis included visual inspection, microscopic examination, mechanical testing, and chemical testing where appropriate.

The study results showed that the majority of device returns were due to gel fracture, bubbles, and/or air voids, without rupture (about 24.2%). However, these problems were perceived as minor flaws due to the fact that all implants were found to be intact with no apparent failures. Similarly, gel-related observations accounted for 12.2% of devices returned. Devices with evidence of surgical damage and possible surgical impact also made up a relatively large percentage of devices with failures (about 17.1% of all devices returned). Approximately 24.3% of the total number of devices returned to the laboratory were determined to be essentially intact and no failure found.

Stability/Shelf Life Studies

Real-time and accelerated sterility data submitted supports the proposed five-year shelf-life for dry heat packaging and satisfies Section 32 (4)(i)(i) of the Canadian *Medical Devices Regulations*.

3.4.5 Clinical Effectiveness and Safety

The clinical study was designed as a ten-year prospective multi-centre clinical trial. Complete data was provided through three years post-implantation. A total of 941 patients participated from three cohorts: augmentation (492), reconstruction (225) and revision (224). A total of 150 augmentation patients, 96 reconstruction patients, and 70 revision patients were enrolled in the serial MRI study. During this report period, two MRI visits were recorded through the three-year follow-up.

Inamed also provided a rupture and complication report on women in the Danish Registry who underwent breast implant surgery with the Style 410 Silicone-Filled Breast Implants. The Danish Registry for Plastic Surgery gathers information on pre-, peri-, and post-operative data for women undergoing breast surgeries.

Details of a Swedish MRI study with Style 410 implants provided further long-term data on the prevalence of asymptomatic rupture 5-9 years post-implantation. This multi-centre, cross-sectional, prospective study included a total of 144 patients (286 devices).

By the end of the follow-up of the Style 410 Cohesive trial 86.6% of augmentation, 89.2% of reconstruction, and 87.2% of revision patients had been evaluated through to three years. To estimate the risk of complications following implantation, Kaplan-Meier survival analysis was conducted on the time-to-first-occurrence of each event at 1, 2, and 3 years post-implantation. Quality of Life (QoL) measures were recorded using a repeated-measures analysis of variance at baseline/pre-implantation and at two years post-implantation.

Complications

Kaplan-Meier first time to occurrence cumulative complication rates are provided below by study cohort. Rates are provided by patient.

The complication rates in the augmentation cohort were low with the highest incidence being implant malposition (2.6%), followed by capsular contracture (1.9%), and swelling (1.8%). All other complications were below a rate of 1.5% per patient. The overall risk of any complication in the augmentation study cohort through to three years was 19.1%. Most complications in the augmentation cohort were resolved at the three-year follow-up (77.0%). More than one quarter (28.4%) of all complications were resolved without treatment, 44.8% were resolved with non-surgical treatment, and in 26.9% surgical treatment was necessary. The re-operation rate was 12.5%. The most common reasons for re-operation were implant malposition (18.1%) and patient request for style/size change (16.7%).

The three most frequent complications in the reconstruction cohort were asymmetry (8.7%), followed by capsular contracture (5.9%), and implant malposition (4.9%). There were a total of ten complications $\geq 1.5\%$, and the overall risk of any complication in the reconstruction study cohort through to three years was 40.5%. Most complications in the reconstruction cohort were also resolved at the three-year follow-up (73.5%). More than half (54.2%) of these complications resolved through non-surgical treatment, 8.3% without treatment, and 37.5% with surgical treatment. The re-operation rate was 31.8% by patient, and reasons for re-operation were mainly due to scarring (27.0%), implant malposition (14.6%), and patient request for style/size change (12.4%).

The three most frequent complications in the revision cohort were capsular contracture (5.2%), followed by asymmetry (4.7%), and implant malposition (4.2%). There were a total of eleven complications $\geq 1.5\%$, and the overall risk of any complication in the reconstruction study cohort through to three years was 32.9%. Most of these complications (74.0%) were resolved

in the revision study cohort by the three-year follow-up visit. More than half (57.4%) of all complications were resolved with non-surgical treatment, 11.1% without treatment, and in 31.5% surgical treatment was necessary. The re-operation rate was 20.6%. The most common reasons for re-operation in the revision cohort were due to capsular contracture (17.9%), implant malposition (12.5%), and scarring (12.5%).

Data from the Danish Registry indicated that of the 164 augmentation implants, 14.0% of patients experienced a complication and 6.7% underwent surgery for the complication. The most common complications for augmentation patients were implant displacement and revision. Of the 325 reconstruction implants, 21.5% of patients experienced a complication and 9.9% underwent surgery for the complication. The most common complications for reconstruction patients were implant displacement and revision. There was no occurrence of capsular contracture (Grade III/IV) in the augmentation patients to date and was reported in only 4.0% of the reconstruction patients. The average implantation time for these women was 3.2 years.

Overall, the Style 410 implants improved upon past saline breast implant and Core standard gel studies in terms of overall complications.

Rupture Rates

Style 410 Core Study

Three-year rupture rate data were similar to the rates expected according to the Inamed round implant rupture data, suggesting that the cohesive gel can be imaged with the same imaging techniques as the responsive gel implants. The rupture occurrences gathered from the MRI and non-MRI study groups demonstrate that MRI was the primary means of detecting rupture and all of the ruptures detected were silent ruptures (both MRI and non-MRI study groups). However, the majority of the ruptures (3 out of the 5 implants) remain unconfirmed. Patient follow-up will continue to be conducted on these patients, however current data does not indicate unusual symptoms. As of the three-year follow-up, there were no extracapsular ruptures confirmed in a Style 410 implant. It is likely that this trend has continued due to the degree of cohesivity of the Style 410 gel.

Of the patients undergoing either unilateral or bilateral augmentation, 150 patients (299 implants) were enrolled in the MRI sub-study. Compliance at the first and second serial MRIs was about 84% (84.2% and 84.1% at year 1 and year 3, respectively). At three years, one implant in one patient was affected by silent rupture. No patients were

known to be affected by rupture in the remaining non-MRI cohort (342 patients). Therefore, the rupture rate (including unconfirmed ruptures) was 0.7% in the MRI sub-cohort or 0.2% in the overall augmentation cohort.

Of the patients undergoing cohesive gel implantation surgery for breast reconstruction, 96 patients (161 implants) were enrolled in the MRI sub-study. There was 95.0% and 86.9% compliance for the first and second serial MRIs, respectively. In the MRI cohort, there was one implant with a confirmed rupture at three years. The patient has not been seen for follow-up at the time of the last study update, but will be examined for patient satisfaction, complications, and CTD signs and symptoms at her next follow-up visit. The overall rupture rate in the reconstruction MRI sub-study cohort was 1.3%. Of the remaining 129 non-MRI reconstruction patients, no patients/implants were known to be affected by rupture. The overall rupture rate in the reconstruction cohort was 0.6%.

Patients undergoing serial MRI in the revision MRI sub-study (70 patients, 131 implants) demonstrated a 90.9% compliance rate (by patient) after the first serial MRI and an 88.7% compliance rate after the second MRI. At three years, two implants in one patient were affected by rupture. These two implants remain unconfirmed for silent rupture. The patient's rupture was asymptomatic. No symptomatic ruptures were found in the MRI sub-study, resulting in an overall rupture rate in this sub-study cohort of 1.5% by patient. Of the remaining 154 non-MRI patients, there was one implant affected by rupture, which was confirmed for silent rupture, resulting in an overall rupture rate in the non-MRI group of 1.0% by patient. The patient with the confirmed rupture was seen one day following rupture confirmation, at which time no local complications were observed. No evaluations of CTD signs and symptoms and/or patient satisfaction after confirmed rupture have been made to date for this patient. The overall known rupture rate at three years in the revision cohort was 1.0% by patient for both confirmed and unconfirmed ruptures.

Other Rupture Studies

There were no patients in the Danish Registry who experienced a rupture.

The Swedish MRI study reported no evidence of rupture in 99% of implants. Evidence of rupture was seen in 0.3% (1) of implants with an additional 0.7% (2) that were indeterminate. All indeterminate evaluations were considered ruptures such that the worst case rupture prevalence was 1.0%. These results are based on MRI monitoring for silent rupture.

Long-term Predicted Rate of Rupture

A mathematical model of expected rupture rates was generated based on data from the Style 410 studies as well as a saline implant study. The ten-year rupture rate estimate for the Style 410 implants was predicted to be no higher than 13.5%.

Risk Factors Analysis

Five critical clinical outcomes were examined by the Cox proportional hazards regression analysis: re-operation, implant replacement/removal, implant rupture, capsular contracture, and infection. The following eleven patient, device, and surgical characteristics were selected as potential risk factors: patient age, device height, device projection, device size, anesthesia, surgical facility, incision site, implant placement, pocket irrigation with an antibiotic, pocket irrigation with betadine, and pocket irrigation with a steroid.

Some significant differences were found among the variables, however these results were not consistent across study cohorts. Currently, there is no medical literature to confirm correlations among any of the variables, and differences in relationships have varied upon yearly updates to the data. For these reasons, the full significance of the co-relationships between variables found through this analysis has not been determined and will require further study to be thoroughly assessed.

Effectiveness and Patient Satisfaction

Inamed used a variety of quality of life (QoL) measures to assess effectiveness in each study cohort of the Core Study, including general health-related concepts, self-concept, self-esteem and body esteem. QoL data was measured pre-implantation and at each follow-up visit 1 and 2 years post-implantation. QoL questionnaires were asked of the augmentation and reconstruction cohorts, however only patient and physician satisfaction following each follow-up visit was conducted in the case of the revision study cohort. The QoL data to two years demonstrated mainly positive improvements over both the augmentation and reconstruction cohorts compared to baseline pre-implantation scores. Significant improvements to QoL outcomes were seen in the augmentation study cohort in the areas of specific self- and breast-related concepts such as physical self-concept, sexual attractiveness, satisfaction with breasts, how well breasts matched, satisfaction with breast size, shape, and feel. In addition to improved self image, social relations and improved daily living were noted according to the Rowland Expectation measures.

Reconstruction patients also experienced mainly significant improvements in QoL. According to the general health concepts scale, patients reported a statistically significant decrease in health transition. According to the specific self- and breast-related concepts measures, reconstruction

patients demonstrated statistically significant improvements in satisfaction with breasts, how well breasts matched, satisfaction with breast size, shape, size, and feel, and experienced overall improvements in well-being according to the Rowland Expectation scale.

QoL data demonstrated mainly positive improvements in both augmentation and reconstruction cohorts compared to baseline pre-implantation scores. Satisfaction with surgery rates from both patients and physicians were also provided. In each of the three study cohorts most patients and physicians (over 91% and 93%, respectively) expressed being satisfied with the implantation procedures using the Style 410 implants. Of those physicians indicating dissatisfaction, reasons were mainly due to capsular contracture, implant malposition, asymmetry, and breast shape. Reasons for dissatisfaction from patients included capsular contracture, implant malposition, breast shape, and desire for implant size/style change.

CTD Signs and Symptoms and Other Events

Breast disease, reproduction, and lactation issues were not found to significantly increase in any of the study cohorts from pre-implantation through to three years. Rates of confirmed Connective Tissue Diseases (CTD) were also not found to significantly increase by the three-year follow-up. Inamed has also collected supplemental data on CTD signs and symptoms, although not originally part of the Core Study protocol. Inamed's analysis over the course of the Core Study follow-up looked at whether or not signs and symptoms increased after implantation beyond what is expected due to aging. Inamed determined that according to the information gathered across domains, some signs and symptoms tend to increase from pre- to post-implantation and not all of the changes can be attributed to aging. However, conclusions could not be drawn from these findings since the Core Study was not designed to assess CTD signs and symptoms. The sample size in the Core Study was insufficient to track such trends and lacks appropriate study controls.

Clinical evidence in this area is supplemented by evidence-based literature studies and reports on Inamed's smooth and textured silicone gel-filled breast implants, and breast implants in general, as provided by the manufacturer.

Literature Studies

Inamed submitted a review of potential problems that have been associated with breast implants in the literature (cancer and benign breast disease, CTDs, including fibromyalgia, interference of device with mammographic detection of tumors or rupture, neurological disease, ability to lactate, second generation effects, and safety of breast milk). These and other potential health issues have been intensively reviewed by the American-based Institute of Medicine (IOM) and the UK-based Independent Review Group (IRG). These reviews have been confirmed by

studies since, including several meta-analyses, concluding that no major ill health effects are causally associated with breast implants. For the most part the literature has not found any increased health risks for women with silicone breast implants, however, some recent findings have suggested women with breast implants are more prone to suicide and one study has suggested a relationship among women with breast implants and low birth weight of their offspring. In the literature review provided by Inamed, the bulk of the scientific literature does not agree with these linkages and that confounding reasons pertaining to suicide and to the occurrences of low birth weight children were not presented in such studies.

Although no causal association has been established in the medical literature between breast implantation and suicide, Inamed has included a contraindication in the physician labelling for patients presenting with body dysmorphic disorder or other psychosis, and a precaution for patients presenting with depression and/or an eating disorder, to be treated prior to considering breast implantation surgery. The patient labelling will also include a statement to the same effect recommending resolution of psychiatric disorders such as depression and eating disorders prior to making a decision regarding breast implantation. A literature summary specific to the Style 410 product and like cohesive gel products was produced by Health Canada and was included in the information reviewed by the Expert Advisory Panel (EAP). From the literature reviewed, the Style 410 implants appear to have similar clinical outcomes as those achieved with less cohesive silicone gel-filled breast implants. However, the underlying difference is focused around surgical techniques of cohesive gel implantation, and the problems have appeared to be mainly inherent to implant choice and patient suitability (e.g. tissue coverage). These issues may be common to all breast implantations but especially important in the case of breast implants with more cohesive gels. In addition, implant rotation and malposition may be of greater concern due to the fact that these implants are shaped, and may require a larger incision since the implants may be less malleable than less cohesive gel implants.

Inamed's clinical studies also demonstrated that the Style 410 implants do not interfere with mammography. An independent literature review by a radiologist supported the validity of MRIs in screening for rupture of the Style 410 implant based on empirical evidence and the use of certain techniques, such the Eklund Technique. This technique involves more images to maximize the evaluation of breast tissue in patients with breast implants and can also be used in women with these more cohesive gel implants.

3.4.6 Software Validation Studies

The Inamed Style 410 Silicone-Filled Breast Implants do not contain or require any software.

3.4.7 Labelling

The three-year clinical study data is presented in the physician and patient labelling information for Inamed's Style 410 implants and it was expressed that the long-term safety and effectiveness of these implants have not yet been established. However, Inamed is monitoring the effects of implant rupture, re-operation, implant removal, breast disease, and other local and systemic complications over a ten-year study period. In addition, the expectations related to re-operation rates, complications, and surgical outcomes through to year three clinical trials were clearly outlined in the patient labelling for each study cohort in separate booklets. Each booklet contains cohort-specific clinical data and post-implantation follow-up information, where applicable.

In addition to the EAP's recommendations regarding the mental health status of patients considering breast implantation surgery, information regarding possible effects of breast feeding and the risks of CTDs and other rare adverse events have been addressed in the labelling.

It was also recommended by the EAP that MRI should be used to investigate breast implant signs and symptoms and not be used for scheduled or periodic screening for breast implant integrity (ex. semi-annual screening), citing a lack of reliable scientific evidence supporting the use of MRI for silicone breast implant rupture screening every one to two years. Instead it was concluded that assessment of silicone gel-filled breast implants should be at the discretion of the plastic surgeon in consultation with the patient, and preferably be based on new breast symptoms or signs. The EAP placed a strong emphasis on a proactive approach to implant monitoring on the part of both the patient and her consulting physician. Women are recommended to follow generally recognized guidelines for breast health, which include regular breast self-examinations. The panel also came up with a six step process to breast implant monitoring, which has been adapted by Inamed in their patient labelling.

Inamed's patient brochure entitled, "Patient Planner", includes a signature block at the beginning of each labelling section for augmentation, reconstruction, and revision patients. This section is a component to the informed consent process, which includes the patient's review of the patient brochure (also known as the patient labelling). It also provides the physician the opportunity to review key ideas listed on the form with the patient to ensure they have a firm understanding of the risks and benefits prior to proceeding. The form includes a place for both the patient and physician to sign their names, signatures, and the date. Inamed has agreed to the EAP's recommendations that the labelling not be enclosed in the sterile box with the product so that it can be available for patients to consider before surgery and to provide identification cards with model and serial numbers to the patient to serve as a tracking tool for these devices.

The labelling material provided for the Inamed Style 410 Silicone-Filled Breast Implants was reviewed and found to meet the requirements of Section 21 of the *Medical Devices Regulations*. Focus groups may be used to determine the effectiveness of the current labelling and patient planner.

3.5 Risk/Benefit Assessment

A standard risk assessment (EN 1441) was used to assess the risks of the Style 410 implants. Possible hazards analyzed were functional or mechanical failure, diffusion of filler, extractable materials from shell, implant movement, and theoretical hazards (e.g. autoimmune disorders, connective tissue disorders, cancer, etc). All risks analyzed were estimated as low risks, therefore it is concluded that the Inamed Style 410 Silicone-Filled Breast Implants meet the acceptance criteria and together with the risk analysis have been deemed safe and effective for their intended use.

3.6 Decision

Based on the Health Canada review of data on quality, safety and effectiveness, Health Canada has granted a licence with conditions in accordance with *Medical Devices Regulations*, Section 36(2) to Inamed Corporation for their Style 410 Silicone-Filled Breast Implants. This licence is subject to the following conditions:

- 1) The manufacturer will continue the data collection, and provide annual updated reports from the ongoing Core clinical study of 1000 patients through to ten years, including:
 - a. First time of occurrence and cumulative incidence of complications recorded at follow-up visits containing reports of confirmed and unconfirmed connective tissue disorders (including a summary of any rheumatological reports) or new diagnoses of cancer and Cox regression analysis of complications;
 - b. Patient and physician satisfaction measures;
 - c. A summary of data with key complications (such as rupture), device removals with or without replacement, subdivided by device type, shell type and patient type;
 - d. A detailed incidence report of rupture (symptomatic and asymptomatic in both MRI and non-MRI study cohorts), incidence of intracapsular and extracapsular rupture, and any reported signs and symptoms associated with the occurrence of rupture (confirmed or unconfirmed).

