Inamed Corporation's Silicone-Filled Breast Implants (P020056)

April 12, 2005

FDA Presenters

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Background, Device Description, & Preclinical Testing Overview

Samie Allen

Background

- Dec 2002 – Inamed submitted PMA P020056
- Oct 2003 – PMA presented to Panel
  - 494 aug, 221 recon, and 225 rev
  - Physician – complete 2-year; partial 3-year
  - MRI data – complete 1-year; partial 3-year
  - 9 to 6 Panel vote for approvable w/conditions
- Jan 2004 – FDA issued not-approvable letter
  - Rupture rate over the lifetime of the device
  - Health consequences of implant rupture
  - Modes and causes of rupture

Background (cont.)

- Aug 2004 – Inamed submitted response
- April 2005 – return to Panel
  - Physician – complete 3-year; partial 4-year
  - MRI data –
    - Complete 1 and 3-year for aug
    - Complete 1-year and partial 3-year for recon and rev

Device Description

- Styles 10, 15, 20, 40, 45, 110, 115, 120 & 153
- Round & shaped
- Range of profiles
- Smooth & textured surfaces
- Single lumen except Style 153
- Components: shell, patch, filler, & silicone adhesive

Preclinical Testing

- Modes and causes of rupture
- Gel bleed
- Shelf life

Modes & Causes of Rupture

- Retrieval studies of explanted devices
- Physical property / crosslink density testing
- Assessment of manufacturing processes
- Assessment of surgical techniques
- Review of literature

Modes & Causes of Rupture (cont.)

Inamed's Retrieval Program Analysis:

- Explanted devices received through 3/31/04
- 442 devices: 40 Core Study and 402 Adjunct Study devices
- 287 devices intact, 20 excluded
- 135 available for analysis

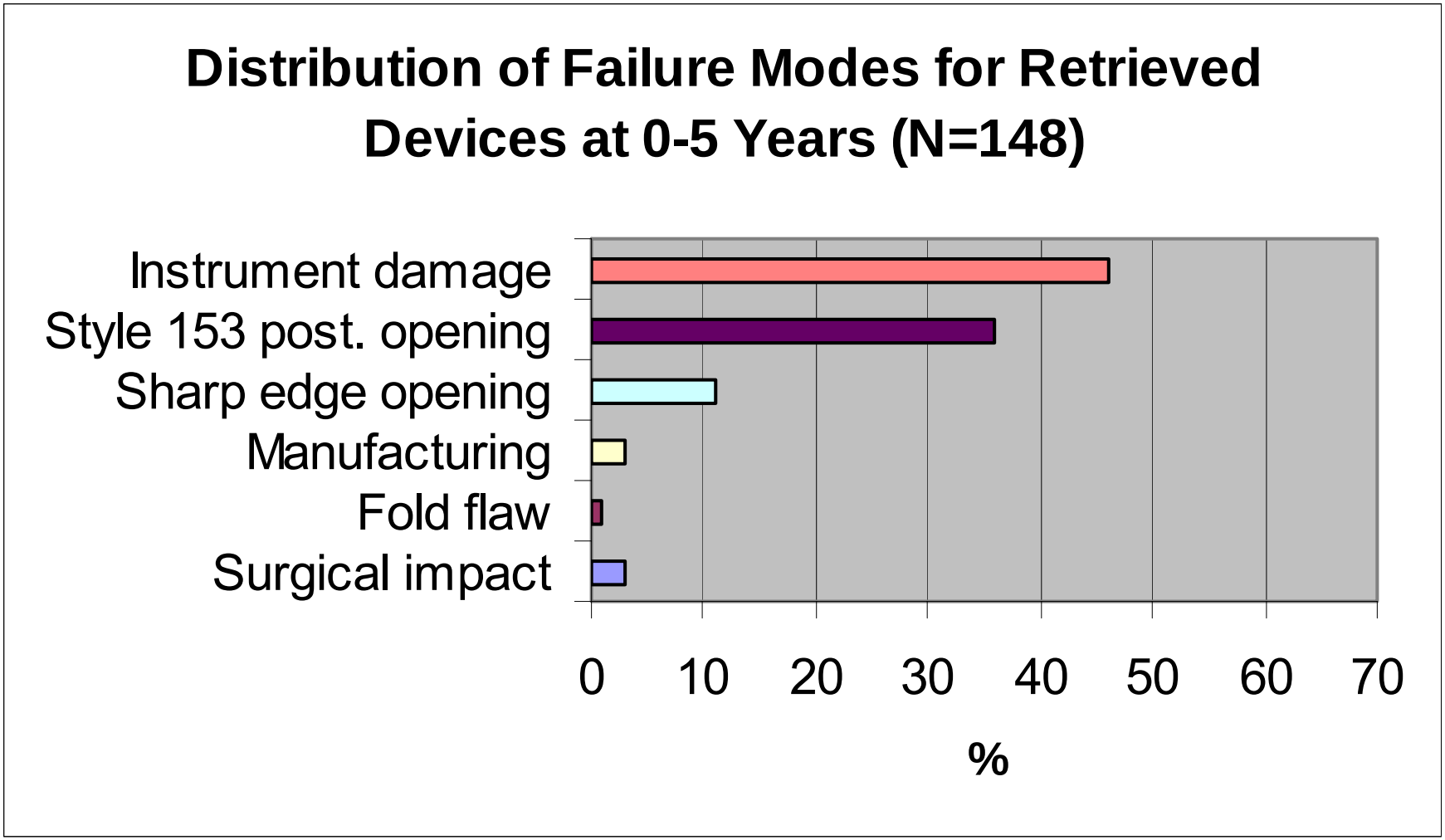
Modes & Causes of Rupture (cont.)

Failure Modes	**N**
Surgical damage	63
Style 153 posterior opening	48
Sharp edge opening *(cause unknown)*	12
Surgical impact	5
Manufacturing	4
Style 153 bladder separation	2
Fold flaw	1
Total	135

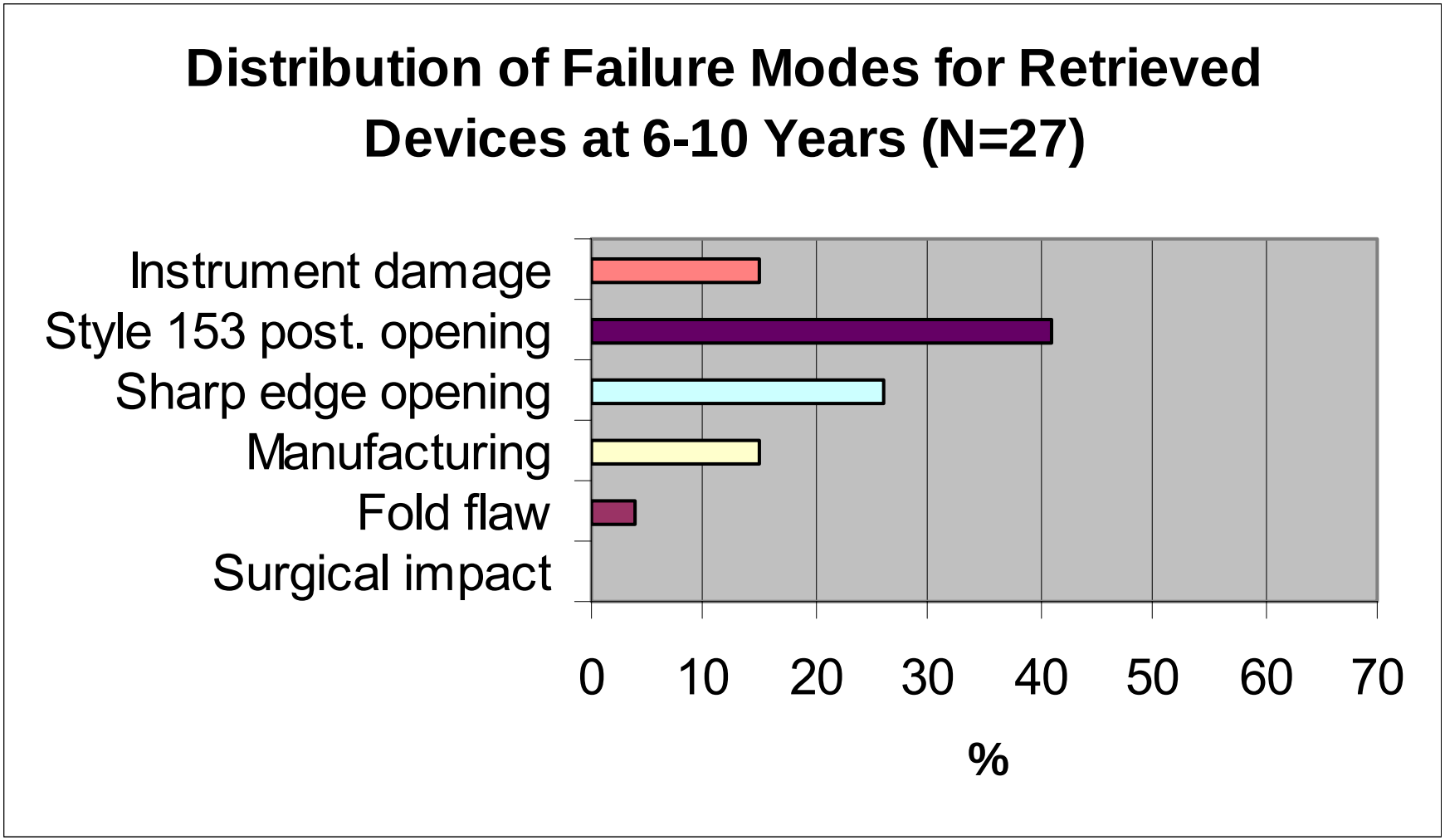
Modes & Causes of Rupture (cont.)

Supplemental Analysis of Failure Modes	# (%) of Retrieved Device		
	0-5 yrs	**6-10 yrs**	**>10 yrs**
Instrument damage	68 (46%)	4 (15%)	0 (0%)
Style 153 post. opening	54 (36%)	11 (41%)	0 (0%)
Sharp edge opening *(cause unknown)*	17 (11%)	7 (26%)	6 (67%)
Manufacturing	4 (3%)	4 (15%)	1 (11%)
Fold flaw	1 (1%)	1 (4%)	2 (22%)
Surgical impact	4 (3%)	0 (0%)	0 (0%)
Total	148	27	9

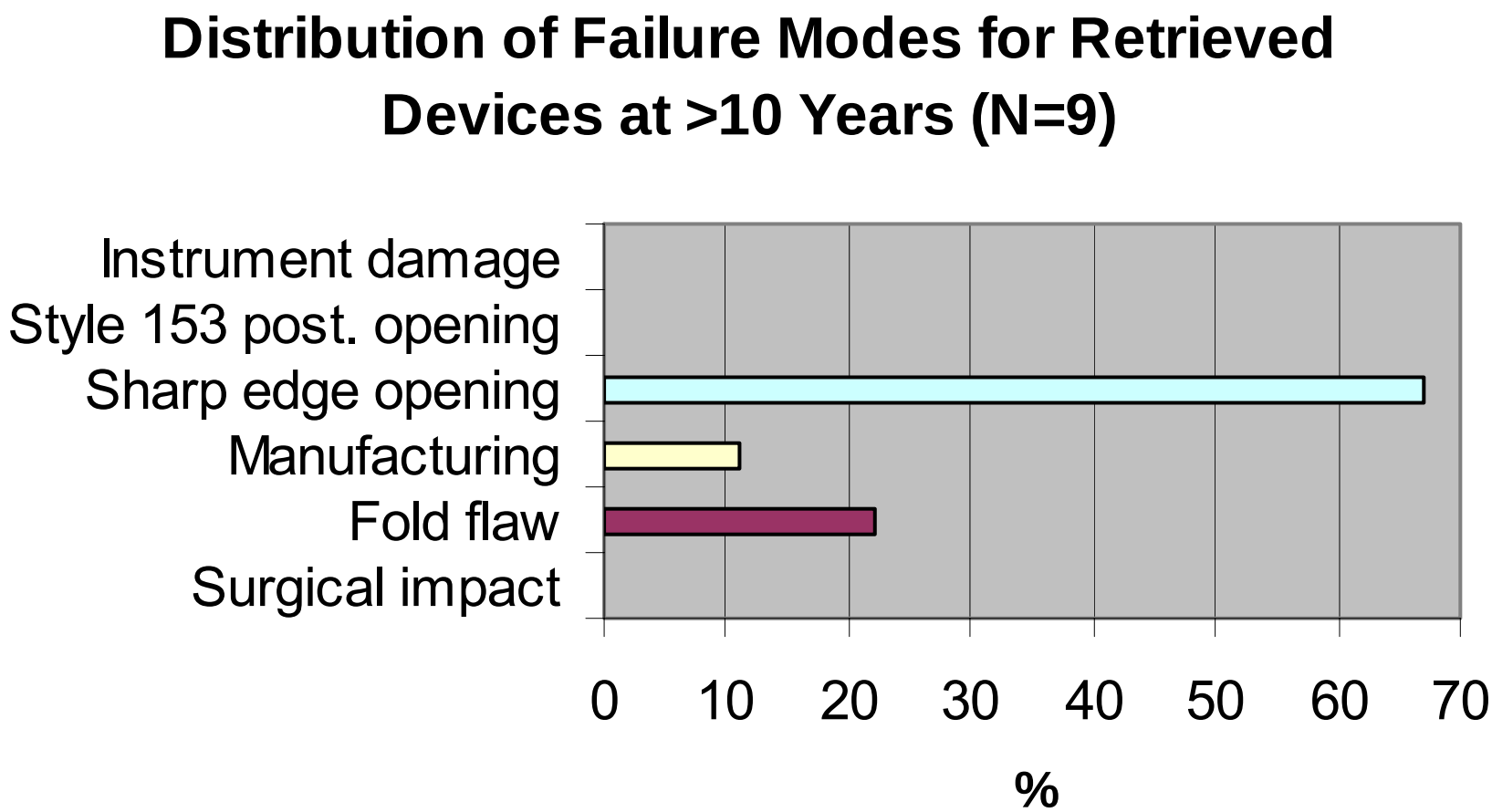
Modes & Causes of Rupture (cont.)



Modes & Causes of Rupture (cont.)



Modes & Causes of Rupture (cont.)



Modes & Causes of Rupture (cont.)

Inamed's Proposed Next Steps:

- Investigate sharp edge openings
- Modify Style 153 design to reinforce patch area
- Research if correlation between surgical factors and device rupture
- Labeling and physician training

Gel Bleed Testing

- 80cc Style 40 implants incubated on 3M silica disks for 8 weeks at 110°F
- Detected cyclic species D8 to D21 and linear species MD6M to MD18M at 8 weeks. Cum. bleed rate was 0.0003 gm/cm^2/wk by week 8
- Issues with testing:
  - No extrapolation of methodology to in-vivo condition
  - Control disk saturation impacts all silicone values
  - No information on binding capacity of 3M disks
  - No analysis for high MW silicone polymers
  - No rate of diffusion for each gel bleed constituent

Shelf Life

- Device and package testing
- 3-year shelf life date on package label

Summary – Preclinical Testing

- Modes and Causes of Rupture:
  - Characterize through ≈10 years
  - Not predictive of lifetime rupture rate
  - Proposed labeling and training to address failures related to surgical procedure
  - Proposed Style 153 design changes
  - Investigate sharp edge openings
- Gel Bleed:
  - Issues with methodology that may warrant new testing
- Shelf Life:
  - Adequate but should continue studies

Rupture Overview- Inamed Silicone Breast Implants

Sahar M. Dawisha, M.D.,
Medical Officer

Silicone Gel BI Rupture

- Silent rupture = asymptomatic to the patient and physician.
- MRI to detect silent rupture.
- Symptomatic rupture = a/w symptoms (i.e. implant flattening, lumps, silicone extrusion).
- Intracapsular rupture = within fibrous capsule.
- Extracapsular rupture = outside the fibrous capsule.

Implant Rupture Questions:

- What is the implant rupture rate over the expected device lifetime?
- How often and when do intracapsular vs. extracapsular rupture occur?
- What is the rate at which intracapsular rupture becomes extracapsular?
- What are the local health consequences of implant rupture?

Core Study: Silent Rupture

- MRI Cohort = screening for silent rupture at years 1, 3, 5, 7, and 9 via MRI.
  - 90% follow-up compliance at 1st MRI.
  - 85% follow-up compliance at 2nd MRI.
  - MRI data at 2nd MRI is partial for recon & rev.

- Non-MRI Cohort = no MRI.
  - Under-ascertainment of silent rupture.

Core Study KM Rupture Rate through 4 years : By-Patient

	MRI	Non-MRI
Aug	3.4% (0.5, 6.3) N = 166	1.1% (0.0, 2.2) N = 320
Recon	20.5% (11.3, 29.2) N = 107	4.9% (0.2, 9.6) N = 113
Revision	10.9% (3.8, 18.1) N = 78	1.7% (0.0, 4.1) N = 138

Core Study Rupture Rate through 4 Years: By-Implant

	MRI N = 663 implants		Non-MRI N = 1119 implants	
	Silent	Sympt	Silent	Sympt
Aug	5 (0.8%)	1 (0.2%)	2 (0.2%)	3 (0.3%)
Recon	17 (2.6%)	1 (0.2%)	4 (0.4%)	0
Rev	8 (1.2%)	0	1 (0.1%)	1 (0.1%)

Core Study: Rupture Details

- 25 implants (in 25 patients) confirmed ruptured at explant through 4 years.
- 16 of these silent from MRI Cohort; 7 silent from Non-MRI Cohort » » » 23/25 (92%) silent ruptures.
- 23 intracapsular.
- 1 extracapsular (aug patient from MRI Cohort).
- 1 detachment of Style 153 lumens (recon pt; MRI).
- No obvious cases of migrated gel: no sampling.
- No cases of intra → extracapsular gel: all removed.

Inamed 10-year Rupture Rate Estimation: Assumptions

- Appropriate to estimate silent rupture rate in Non-MRI using data from MRI group.
- Appropriate to reduce this estimated rate by excluding unconfirmed false positives.
- Appropriate to pool indications.
- Assume rupture rate will remain constant, resulting in straight line for shape of rupture curve.

Rupture Rate: Other Sources

- Adjunct Study data.
  - No assessment of silent rupture.
  - Low follow-up.
- Saline-filled breast implant data.
  - Deflation is symptomatic rather than silent.
  - Differing materials and design.
  - Differing implantation techniques.
- Complaint database.
  - Voluntary.
  - Denominator based on number sold.
- Danish Breast Implant Registry.
  - No rupture but also no MRI screening.

Adjunct Study: Rupture Details

- 99 implants in 99 patients confirmed ruptured at explant.
- 93 intracapsular.
- 6 extracapsular.
  - 3 with silicone gel leaking from incision wound (all recon pts).
  - 3 with migrated silicone gel in axilla: (1 revision aug, 1 contralateral aug, 1 recon—all after 3 years).

Rupture Rate: Danish Literature

- Scandinavian MRI studies of silent rupture
  - Several manufacturers; Augmentation only.
  - Excludes implants removed in first 3 years.
  - Median implant duration: 12 yrs (3-25 years).
  - Rupture prevalence = 32% of implants.
  - ~25% of ruptures extracapsular.
  - Rupture incidence = 8.9 per 100 implants/yr.
  - 56 ruptures: 48 via MRI, 8 at reoperation.

Hölmich, et al., Plast Recon Surg. 2001; 108: 848-858.
Hölmich, et al., Arch Surg. 2003; 138: 801-806.

Rupture Rate: Other Literature

- FDA MRI rupture study
  - Several manufacturers; Augmentation only.
  - Excludes implants removed in first 6 years.
  - Median implant duration: 16 yrs (6-28 years).
  - Prevalence = 55% of implants; 12% extracap.
- Gaubitz MRI study
  - Several Manufacturers; ¾ recon; ¼ aug.
  - Mean implant duration 9 yrs (1- 26 years).
  - Prevalence = 24% of women; 12% extracap.

Brown, et al., Am J Roent. 2000; 175(4): 1057-1064.
Gaubitz, et al. Rheumatol. 2002; 41: 129-135.

Rupture Health Consequences: Core Study

- Local Complications, CTD Signs and Symptoms, Patient Satisfaction.
- N = 25 confirmed ruptured.
- N = 131 confirmed intact.
- Combined indications.
- 30-60% without F/U after explant.

Rupture Health Consequences: Adjunct Study

- Local complications.
- N = 99 confirmed ruptured.
- Complications reported at explant: CC, asymmetry, palpability.
- N = 77 implants replaced.
- Follow-up of 63 patients; 21 w/ complication.
- Complication after rupture: reoperation.
  - Removal with replacement
  - Capsule procedure

Rupture Health Consequences: Literature

- Case reports of local and distant silicone granulomas.
- Silicone in liver via MRS; higher with rupture.
- No statistically significant differences for autoantibodies and self-reported diseases and symptoms 1 year before rupture in Danish women.
- Extracapsular rupture: 6x↑breast hardness.
- Implant rupture: 2x↑pain or change in shape.
- Intracap → extracap: 9% of implants over 2 years.
- Extracap progression: 14% of implants over 2 years.

Hölmich, et al., Plast Recon Surg. 2003; 111: 723-732.
Hölmich, et al., Plast Recon Surg. 2004; 114: 204-214.

Rupture Summary: Inamed Data

- 3-4 years of comprehensive rupture data.
- Most ruptures are silent, diagnosed via MRI.
- Most ruptures are intracapsular: 4-6% extracapsular; 3% migrated silicone gel.
- Data at 3-4 years extrapolated to 10 years.
- Data limited to address intra → extracapsular rupture and silent → symptomatic rupture.
- No statistical associations between rupture and local complications, satisfaction, CTD S/S: lack of statistical power.

Rupture Summary: Literature

- Serial silent rupture data over 2 years.
- Most ruptures are silent, diagnosed via MRI.
- Most ruptures are intracapsular: 25% extracapsular via MRI.
- 9% intra → extracapsular rupture; half a/w trauma.
- 14% extracap → progressive silicone seepage.
- Breast pain and hardness a/w rupture.
- Evidence of silicone outside the breast area.
- Rupture incidence = 9 ruptures/100 implants/year » » » 22,500 augmentation implant ruptures per year in U.S. (2004 rate)

Silent Extracapsular Rupture: Patient History

- 36 Year Old Bilateral Augmentation.
  - Capsulectomy at 10 months in right implant.
  - 1st MRI 4 months later: no rupture.
  - 2nd MRI at 3 years: rupture in left implant
  - Exploratory surgery in left implant 2 weeks later shows free gel in pocket.
  - Silicone extruding through left incision 2 months later.
  - Bilateral implant removal without replacement.
  - No complications reported.

Rupture Issues to Consider

- Whether the data are adequate to characterize rupture rate over time and health consequences of rupture.
- Whether the existing rupture data provide reasonable assurance of safety.
- What to recommend for silent rupture screening method and frequency.

Labeling Issues

- Method and frequency of silent rupture screening.
  - Low sensitivity and specificity of MRI.
  - Frequency of MRI screening every 1-2 years or as recommended by surgeon.
  - Most ruptures as silent not addressed.
- Clinical management of rupture.
  - Recommendation on whether to remove silent ruptured implant is not clear.
- Health consequences of extracapsular gel.
  - No evidence that extracapsular gel causes any symptoms is inconsistent with Danish literature.

Post-approval Issues

- Continue Core Study.
  - MRI discontinuation issues
- Link voluntary registry to rupture warranty program.
  - no clinical postop data collected
- Additional data from Danish Registry or 3rd party (e.g., NIH).
  - 3rd party data source not specified
  - types of analyses not specified
- Physician education/training program.
  - No certification required for product access
  - Rupture screening method and frequency not included

Safety and Effectiveness Information

- Complications other than rupture and benefits as described in Tab 5 of Panel Pack—database closure one year earlier.
- Consider augmentation and reconstruction separately.
- Consider revision as a continuum of augmentation or reconstruction.

Thank You

Difficulties in Predicting Long-Term Probability of Rupture

Pablo Bonangelino, Ph.D.

Sponsor's Approach

- Based on extrapolating an average percent ruptures per year of 1.4%.
- Simply computed 1.4% x 10 yrs to obtain a probability of rupture by year 10 of approximately 14%.
- 1.4% ruptures/year can be questioned.
- The underlying assumption is a constant percentage of ruptures per year out to 10 years.

The Issue: Difficulty in Predicting Long-Term Effects

- Difficulty demonstrated by considering various models for the rate of occurrence of rupture (percentage of ruptures/year).

- Consider three possibilities (out of many):
  - Constant percentage of ruptures per year
  - Linearly increasing percentage of ruptures per year
  - Quadratically increasing percentage of ruptures per year.

- These three models for the percentage of ruptures per year correspond to three survival models.
- It is not known whether any of these models represent the true situation.
- Models give an example of variability.

Available Data

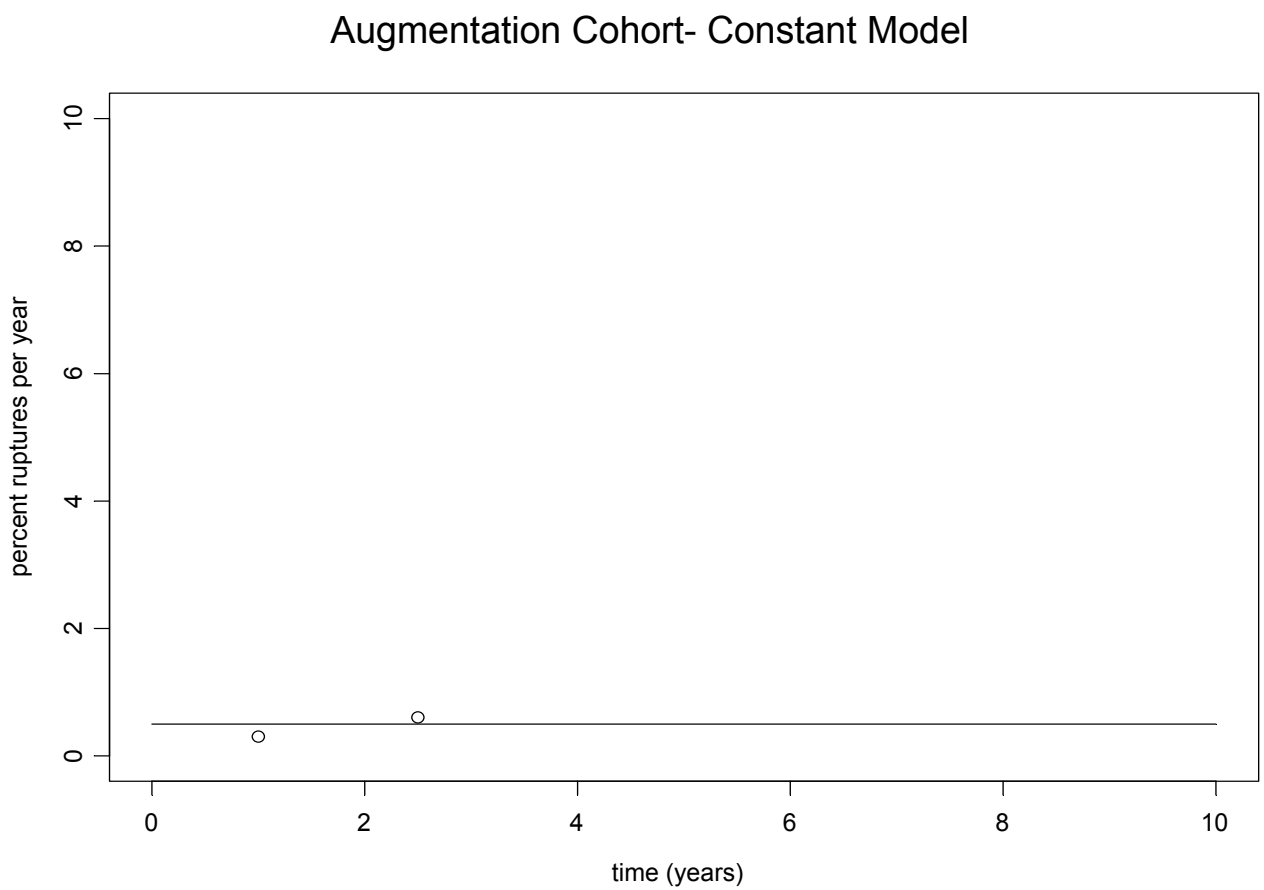
- Kaplan-Meier rates of symptomatic rupture through year 3.
- Kaplan-Meier rates of silent rupture based on MRI data from year 1 and year 3.

- We attempted to fit our models only for the MRI Cohort, as these were the only patients who had active ascertainment of implant rupture.

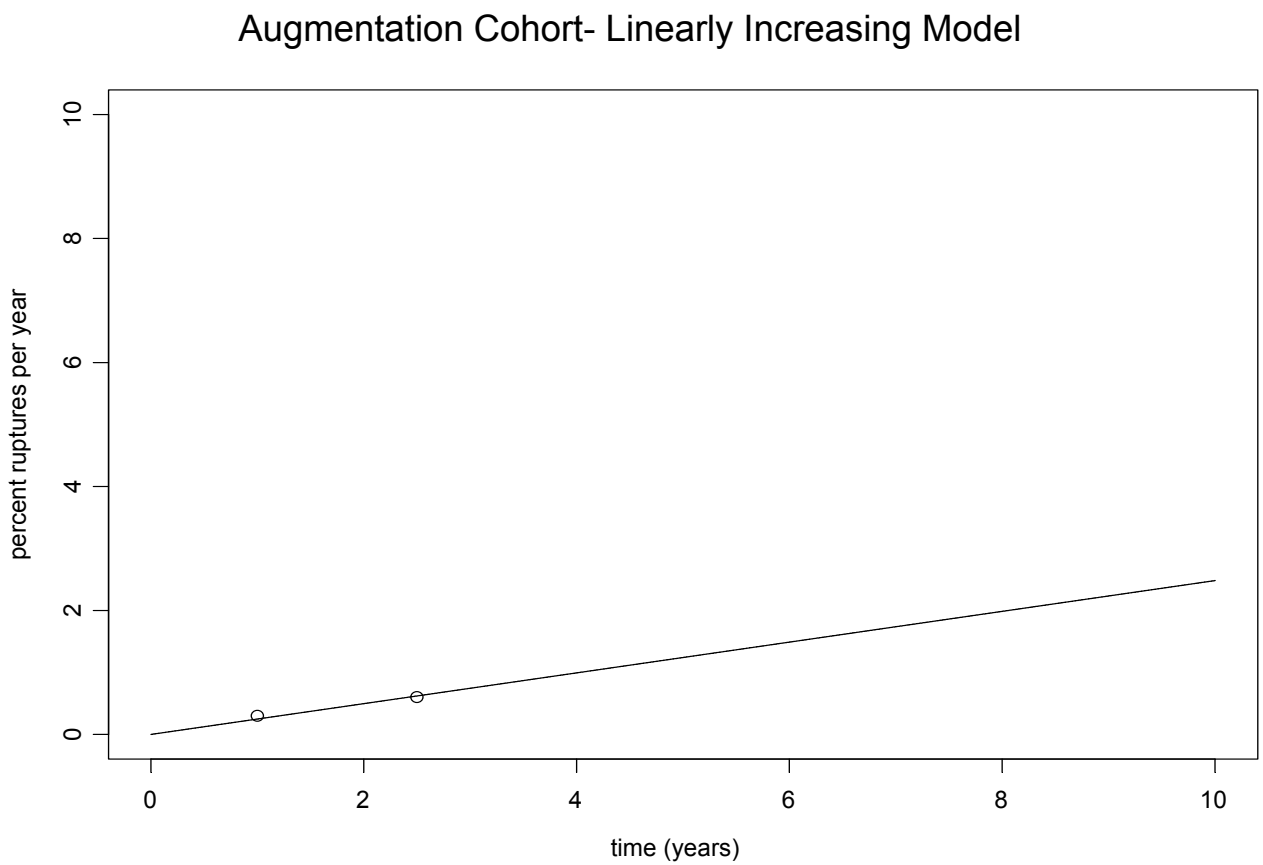
- Note that for silent rupture in the MRI cohort, we really only have two data points, at the year-1 and year-3 MRI. Thus there are only two points on the following graphs to represent the data.

- The example which follows consists of data from the augmentation MRI cohort.

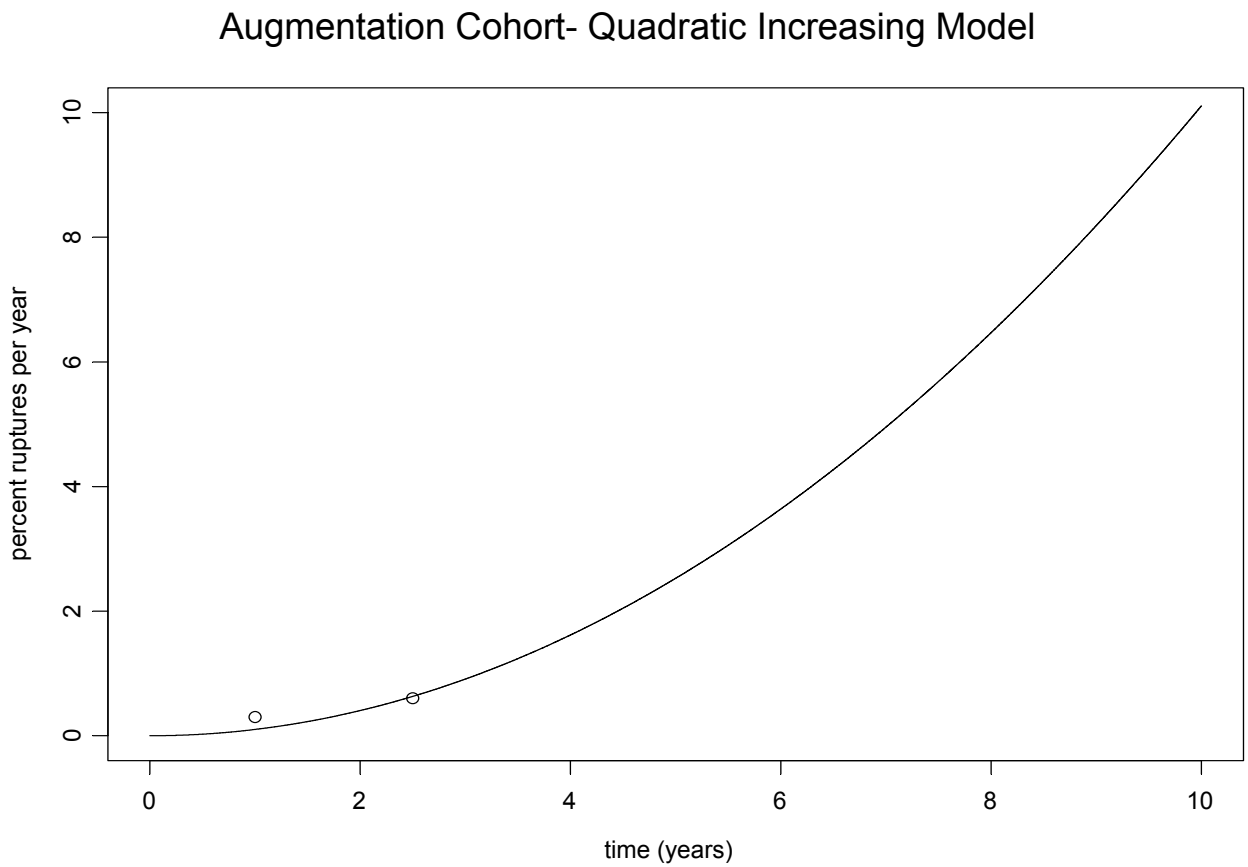
Assumption 1: Constant % of ruptures/year



Assumption 2: Linearly increasing % of ruptures/year



Assumption 3: Quadratically increasing % of ruptures/yr



- All three of our selected models appear plausible.
- With limited data points, any number of models will approximately fit.

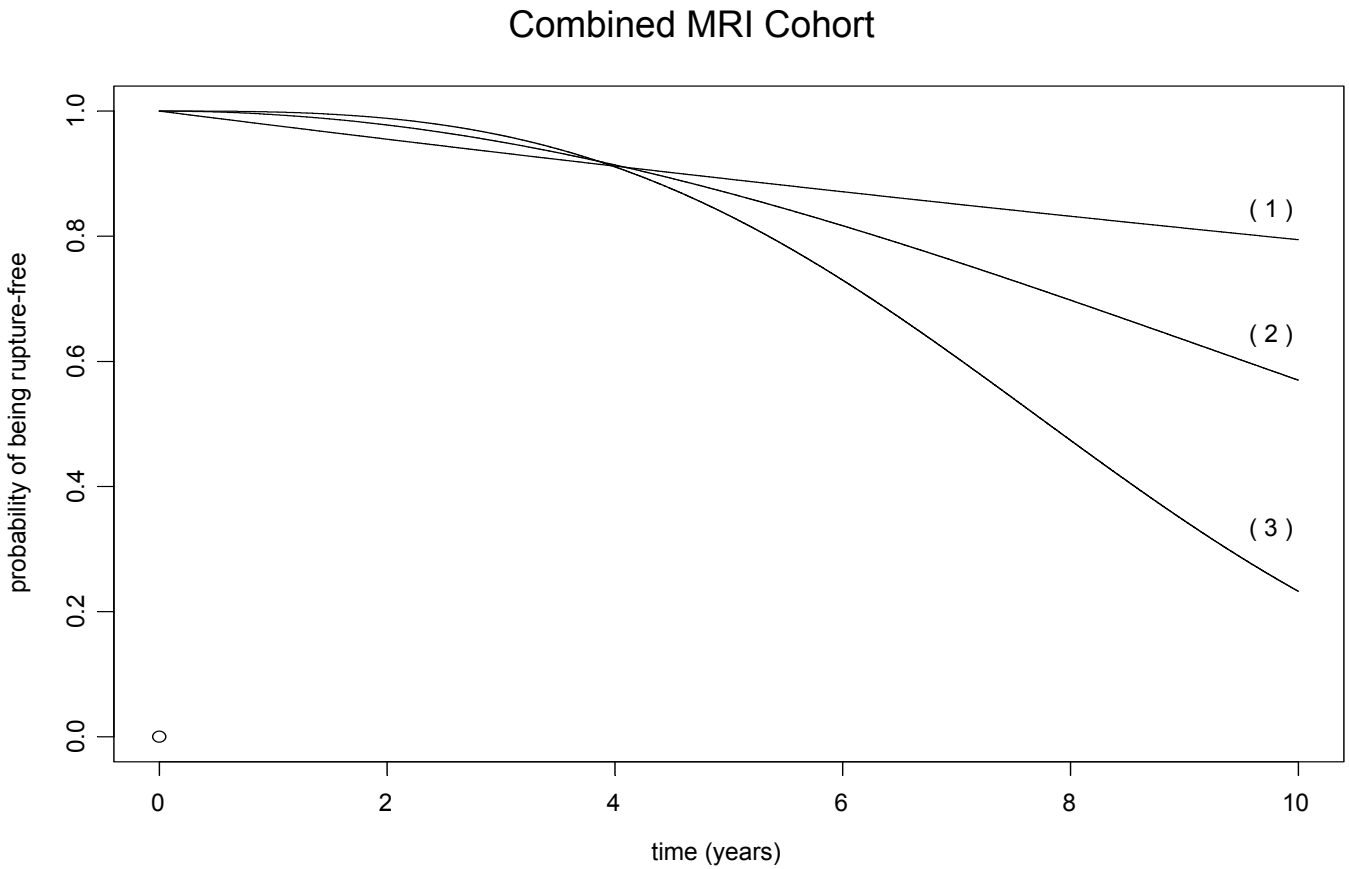
Methods

- We used the three models selected for the percentage of ruptures per year to illustrate the corresponding cumulative probability of implant rupture by year 10.
- Predictions are given for the MRI cohort for augmentation, reconstruction, revision and all indications combined.

Illustration of the Variability in Cumulative Probability of Implant Rupture by Year 10

MRI Cohort- All Ruptures (Silent and Symptomatic)			
Model:	**Constant hazard**	**Linearly increasing hazard**	**Quadratically increasing Hazard**
Augmentation	5% (0%, 10%)	12% (0%, 22%)	29% (0%, 46%)
Reconstruction	39% (22%, 54%)	70% (46%, 83%)	95% (82%, 99%)
Revision	18% (6%, 28%)	38% (15%, 55%)	70% (39%, 84%)
Indications combined	21% (13%, 28%)	43% (29%, 54%)	77% (61%, 86%)

Graphical Illustration of Variability in Probability of being Rupture-free for Three Models:



Summary

- It is difficult to reasonably predict the probability of rupture by year 10 with the available data.

Conclusion of FDA's Presentation

Panel Questions

Panel Question 1

Considering the rupture information provided in their submission, and given that the majority of ruptures for silicone gel-filled breast implants are silent, please discuss whether Inamed has adequately characterized the rupture rate and how this rate changes over the expected lifetime of their device.

Panel Question 2

Please discuss whether Inamed has adequately characterized the consequences of rupture for their device with regard to:

- freq of observed intracapsular gel, extracapsular gel, & migrated gel; destination of migrated gel
- the local health consequences
- silent ruptures → symptomatic ruptures
- intracapsular → extracapsular ruptures.

Panel Question 3

Inamed's proposed labeling includes recommendations for: (1) the method and frequency of screening for silent rupture; (2) clinical management of suspicious and confirmed intracapsular and extracapsular rupture; and (3) potential health consequences of extracapsular and migrated gel.

Please discuss the appropriateness of these recommendations and the extent to which the proposed labeling is supported by the available information.

Panel Question 4

Please discuss whether the plans are adequate to address the issues previously noted by the Panel or any other postapproval concerns that you might have.

Panel Question 5

Please discuss whether you believe that there is reasonable assurance that this device is safe over its expected lifetime for the proposed indications of breast augmentation, reconstruction, and revision.