

# Allergan Experience Post Approval Studies



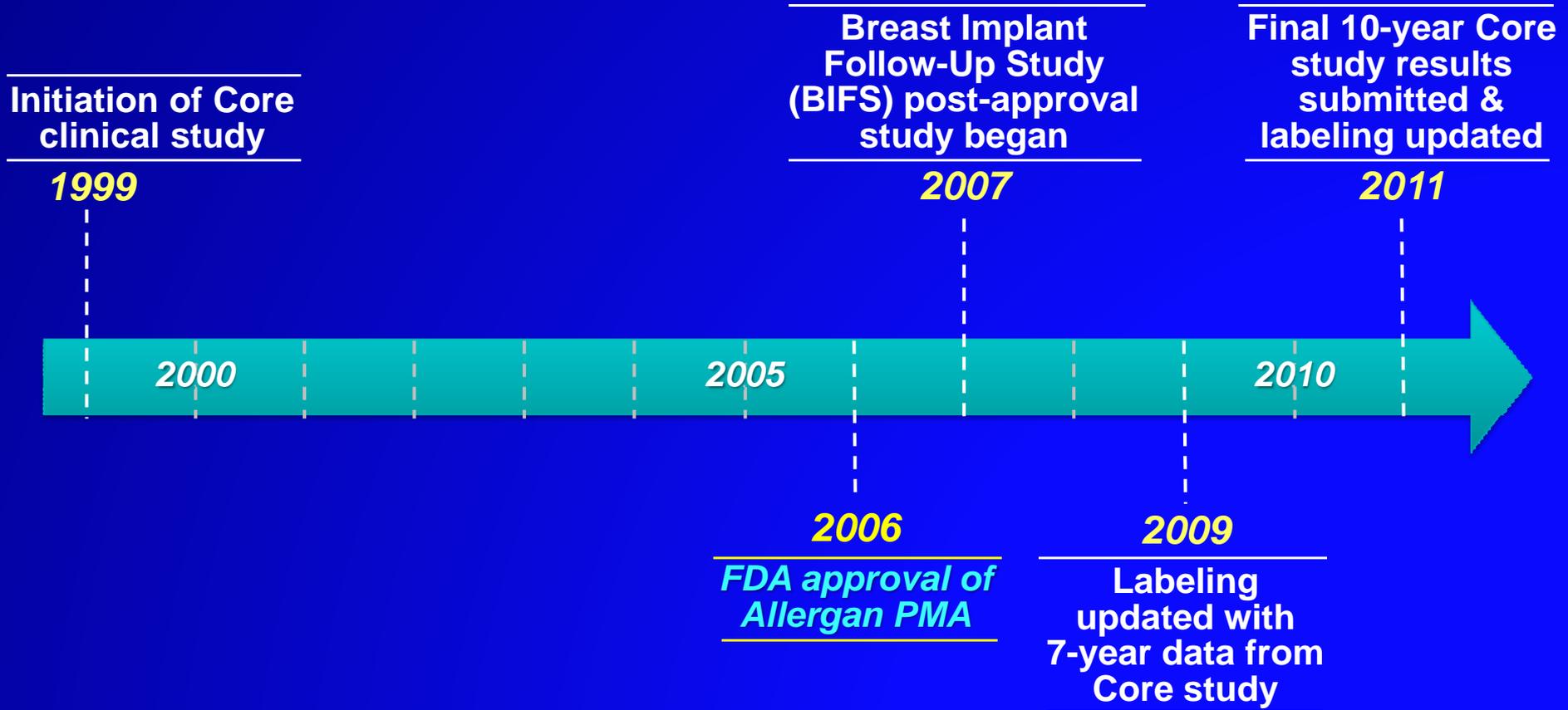
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Chief Medical Officer  
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# Introduction

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- FDA Meeting Objective
  - Designing Post Approval Studies
- Allergan Post Approval Study Experience
- Considerations for future PAS designs

# History of Allergan's Silicone Gel-Filled Breast Implants



# Previous Questions

## 2005 Advisory Panel

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- Local complications such as capsular contracture, infection, repeat surgeries
- Rupture rates
- Reproduction and lactation
- Systemic
  - Cancer (breast, brain, lung, vulvar)
  - Connective Tissue Disorders

# FDA Approval

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- November 2006, FDA approved Allergan silicone breast implants
- Conditions of approval
  - Core Post-Approval Study
  - Large Post-Approval Study (BIFS)
  - Device Failure Study
  - Focus Group Studies
  - Annual Physician Informed Decision Survey
  - Completion of Adjunct Study

**Core Study**

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Pivotal Study

# Core Clinical Study

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- 10-year observational study
- Evaluated endpoints
  - Safety (local complications, implant removal/replacements, reoperations)
  - Effectiveness (cup size change, satisfaction, quality of life)
- Office visits at 0-4 weeks, 6 months, and annually through 10 years post-implant
- MRI subset evaluations at 1, 3, 5, 7, and 9 years after implantation

# Core Patient Enrollment Summary

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- Study Subjects = 715
  - 455 primary augmentation
  - 147 revision-augmentation
  - 98 primary reconstruction
  - 15 revision-reconstruction
  
- MRI Cohort = 264
  - 158 primary augmentation
  - 50 revision-augmentation
  - 51 primary reconstruction
  - 5 revision-reconstruction

# Core Study: 10 Year Cumulative Risk

<b>Augmentation Complication</b>	<b>Final 10-Year Risk By Patient (N = 455) %</b>	<b>Final 10-Year Risk By Implant (N = 908) %</b>
Capsular Contracture	18.9%	13.5%
Breast Pain (early complication)	11.5%	8.6%
Swelling (early complication)	9.2%	7.6%
Implant Malposition (early complication)	6.9%	4.9%
Nipple Complications (early complication)	6.3%	5.3%

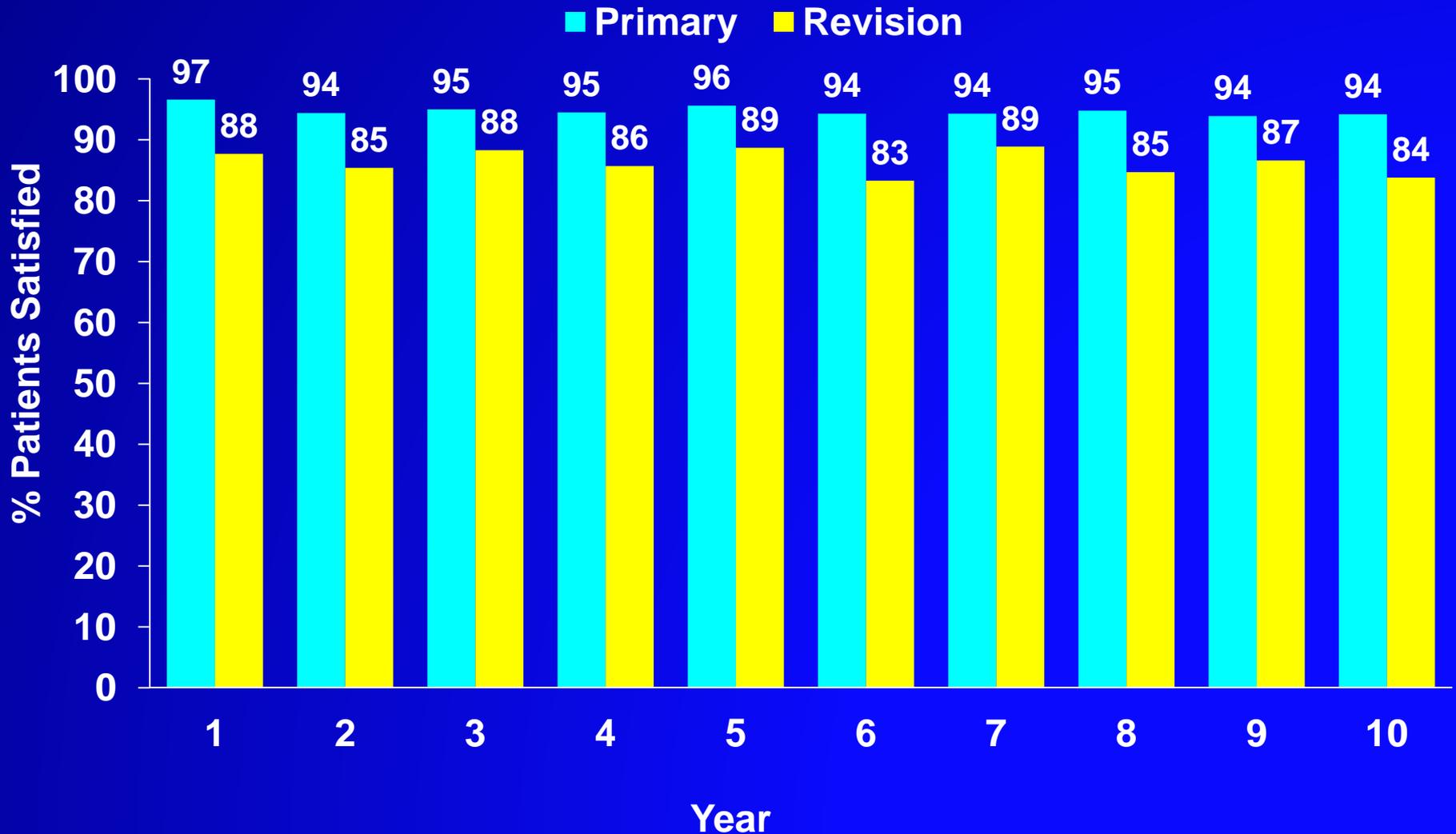
<b>Reconstruction Complication</b>	<b>Final 10-Year Risk By Patient (N = 98) %</b>	<b>Final 10-Year Risk By Implant (N = 127) %</b>
Capsular Contracture	24.6%	22.1%
Asymmetry	23.2%	N/A
Wrinkling	10.2%	9.3%
Swelling (early complication)	7.1%	6.3%
Breast Pain (early complication)	6.8%	6.9%

# Core Study Clinical Events

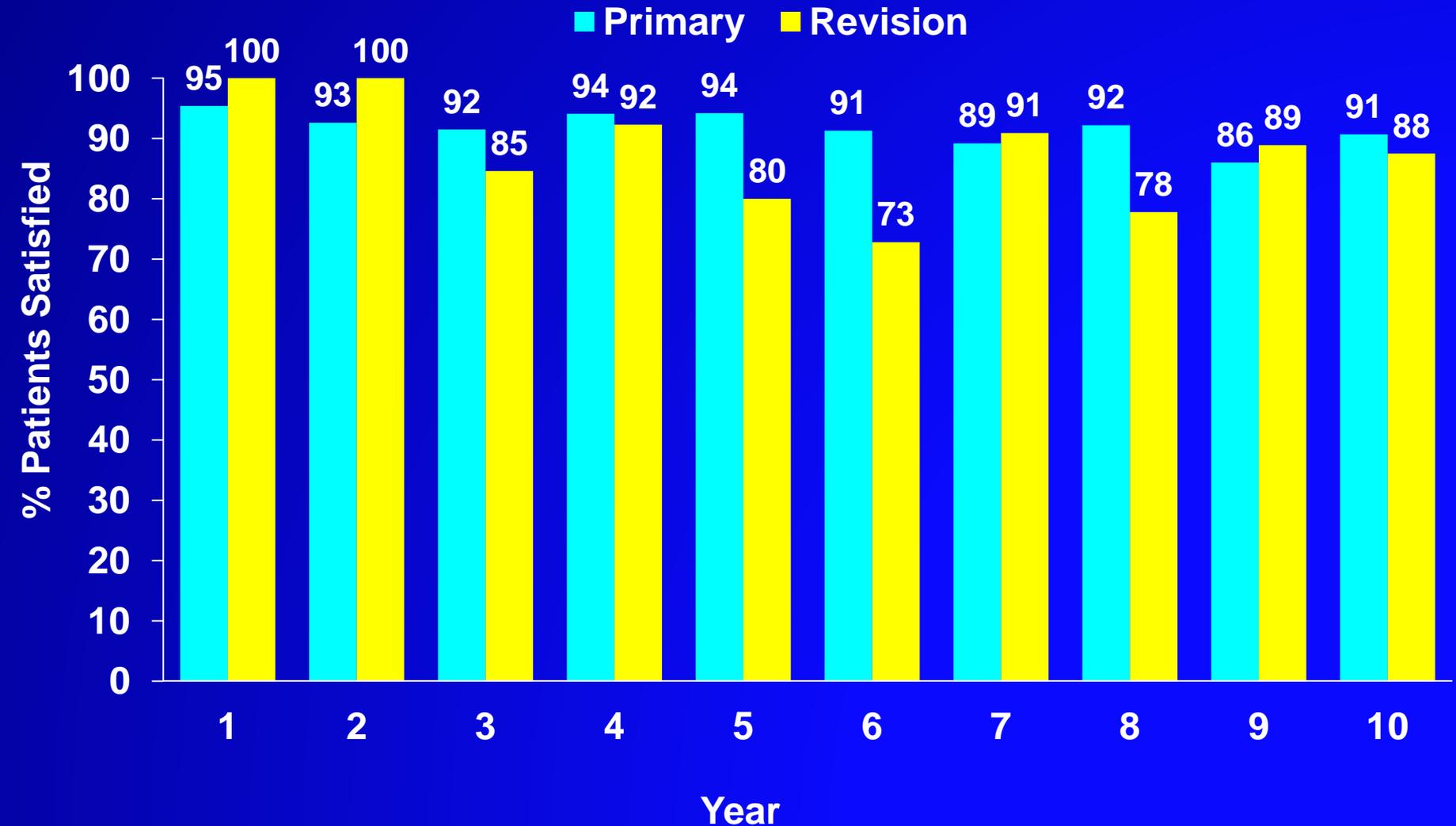
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- Augmentation (455)
  - 5 CTDs (2RA, 2FM, 1RS), 4 breast cancers, 1 suicide
- Revision-Augmentation (147)
  - 2 CTDs (1RA, 1FM), 1 breast cancer, 2 suicides
- Reconstruction (98)
  - 2 CTD (1Undiff, 1RA), 13 breast cancers
- Revision-Reconstruction (15)
  - No CTDs or breast cancers

# Core Study Patient Satisfaction: Augmentation and Revision-Augmentation Through 10 Years



# Core Study Patient Satisfaction: Reconstruction and Revision-Reconstruction Through 10 Years



# Breast Implant Follow-Up Study (BIFS)

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# BIFS: Study Design & Objectives

- 10 year observational study
  - Female,  $\geq 18$  years ( $\geq 22$  for breast augmentation)
  - Annual questionnaire for all subjects
  - Physical exams at 1, 4, and 10 years
- Objectives:
  - Long Term Safety
    - CTD, neurological diseases, cancer, suicide, local complications, reoperations
  - Pregnancy outcomes, lactation issues, offspring
  - Effects on mammography
    - Detection of breast cancer, rate of rupture
  - Effects on satisfaction with breasts and quality of life
  - Compliance with MRI recommendations

# BIFS: Enrollment

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- Enrollment (Optional for subjects)
  - First subject enrolled: February 15, 2007
  - Closed enrollment: March 31, 2010
- Subjects: 56,967
  - 41,325 silicone gel implants (72.5%)
  - 15,642 saline implants (27.5%)
- Sites: 1,026 study sites enrolled

# BIFS: Complication

Complication/Procedure	2 year All Silicone Subjects (N = 12,537)	3 Year All Silicone Subjects (N = 2,808)
<b>Complication Risk Rate</b>		
Capsular Contracture	4.8%	4.3%
Implant Rupture	0.5%	0.5%
<b>Procedure Cumulative Risk Rate</b>		
Reoperation	6.4%	4.0%
Implant Removal with Replacement	2.0%	1.6%
Implant Removal without Replacement	1.2%	1.0%

# Post Approval Study

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The Patients Perspective

# Post Approval Study Enrollment: Patient Perspective

## ■ Why Women Participate

- Compensation
- Fast, easy questionnaire
- Strong interest in the subject

## ■ Why Women Do Not Participate

- Confusing formats or complicated questionnaires
- Misunderstanding of MRI
- Healthy subjects
- Concerns about confidentiality
- Skepticism about motivation

# Post Approval Study Enrollment: Reconstructive Patients Perspective

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- Why they participate
  - more focused on health and safety
  - less motivated by compensation than augmentation patients
  - stronger connection to the idea of helping other women
- Why they do not participate
  - participation reminds them of their illness (something they would like to forget)

# Patient Compliance

<b>Actual observed (Follow-up rate)</b>	<b>Post Implantation</b>		
	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>
<b>Silicone Augmentation</b>	17,896 (66.0%)	10,935 (64.9%)	3,618 (65.6%)
<b>Silicone Reconstruction</b>	3,414 (80.7%)	1,828 (80.8%)	588 (81.2%)

# Lesson from the Focus Groups

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# Allergan Commitment to Compliance: Patient Focus Group

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- Reminders
  - e-mails
  - mailings
  - telephone outreach
  - established preferred method of contact
- Revised website
  - Online questionnaire
  - New options to facilitate interaction
- New direct-to-participant mailer
- Increased call center personnel
- Extended hours and added Saturdays

# BIFS Symbol: “Power of One, Strength of Many”



*“Power of One, Strength of Many”  
appeal to the common motivator among subjects  
to help other women and yet have  
their own voice be heard.*

# Improvement: Direct Mail

**OLD**

**NEW**

- Direct mail piece with revised logo, to differentiate it from “junk mail”

**Compassionate...**

**Empowering...**

**Committed...**

**Your voice has the power to make a difference.**

Complete your BIFS survey online at [www.bifs.us/survey](http://www.bifs.us/survey)

BIFS Support Team Toll-Free 1-888-913-BIFS

# Revised Website

- Interactive emails
- Personalized Welcome and Thank You pages
- Option to:
  - Schedule appointment
  - Questionnaire by phone

The screenshot shows the BIFS website interface with several callouts pointing to specific elements:

- Pop-up window activates on click:** Points to the top navigation bar containing "INVESTIGATOR INFORMATION" and "CONTACT US".
- Emphasis of key messages:** Points to the BIFS logo, which includes the text "Power of strength".
- Multiple Log in options:** Points to the "Participant Login" and "Investigator Login" buttons.
- Contact Info Call Out:** Points to the "Questions? We want to hear from you!" section, which includes the phone number "1-866-619-BIFS (2437)" and the email "bifs@unitedbiosource.com".
- Interactive links:** Points to the footer area containing "Sponsored By ALLERGAN", "© 2010 Allergan, Inc. All rights reserved.", and a "PRIVACY POLICY" link.

The main content of the website includes a header with "INVESTIGATOR INFORMATION" and "CONTACT US", a central image of a woman, the BIFS logo with the tagline "Power of strength", and a main message: "Use the power of your voice to make a difference." Below this, there is a call to action: "Your sister. Your daughter. Your friend or neighbor. Help women who are considering breast implant surgery. Login now to complete your annual BIFS survey!" and a link: "Click here to see a list of participating BIFS physicians".

# Improvements: Emails

- A “click” from the email reminder and subject is taken to the EDC login page to complete the questionnaire

The image shows a screenshot of an email reminder for the Breast Implant Follow-up Study (BIFS). The email is addressed to Elizabeth Pickett and has the subject "It's Time to Complete Your BIFS Survey". The main body of the email features a woman with her arms raised, with the text "Your voice has the power to make a difference!". Below this, there is a call to action: "Click here to complete your BIFS survey today, and help ensure that women continue to have the choice of silicone for their breast implant surgery." A "Login now at: www.bifs.us/survey" button is prominently displayed. To the right, there is a "Unique Registration Code" field with a placeholder "XXXX-XXXX". The email also includes a "Need to update your contact information? CLICK HERE" link and the Allergan logo at the bottom.

Callouts in the image highlight the following features:

- Personalization:** Points to the "Dear <first name,>" text.
- Dynamic hot spots linking to bifs.us:** Points to the "Login now at: www.bifs.us/survey" button.
- Interactive Links & Login button:** Points to the "Click here to complete your BIFS survey today..." text and the "Login now at: www.bifs.us/survey" button.
- Unique personalized registration code:** Points to the "Unique Registration Code:" field.

NEW EMAIL REMINDERS

# Annual Questionnaire Silicone Compliance Years 1, 2, and 3



# Thoughts on Post Approval Studies

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# Post Approval Studies: Closing Comments

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- Core Study and BIFS
  - Cohort, prospective design
  - There were a number of questions at the beginning
  - We now have evidence on these devices and better estimates of risk rates

# Post Approval Studies: Closing Comments

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- Very rare events can be missed with PAS
- Post market surveillance can be a useful tool
  - MDR, ASR, PSR
  - Annual reports with reviews of literature
  - Safety Panel
- Case control designs

# Post Approval Studies Closing Comments

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- New Products
  - Cohort (Prospective) Study
  - PAS
- Product Modification or Product Development based on previously studied devices
  - Should leverage body of knowledge that has been created
  - Question should be aimed at addressing the product differences (new from the old)
  - Build on established knowledge base

# Designing Post Approval Studies: Closing Comments

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- Objective:
  - To assess the effectiveness and safety of a product in the real world as part of a total product life cycle
  - Address questions from the pivotal study

***Benefit our Patients***  
***Clinically Sound and Realistic***

# Allergan Experience Post Approval Studies



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