

1 **Food and Drug Administration Guidance Documents and New Medical Devices:**

2 **The Case of Breast Prostheses**

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1 **Abstract**

2 As pressure mounts on the Food and Drug Administration (FDA) to speed its review process for
3 novel devices, and budgetary pressures further strain its resources, the critical role of guidance
4 documents in assuring consistent, rigorous, and scientifically-grounded review across device
5 types has never been more important. In this article, we use the regulatory experience of one
6 medical device class, specifically implantable breast prostheses, to illustrate the crucial role of
7 FDA guidance documents. We find that the emergence of FDA guidance preceded significant
8 growth of scientific publications around breast prostheses, with 0.30 ± 0.57 papers/year
9 published in the period 1987-2006 compared with 2.27 ± 1.56 papers/year in the period 2007-
10 2017, $P=0.0017$. This illustrates the importance of supporting the FDA to enhance guidance
11 document drafting, revision, publication, and updating to reflect evolving scientific consensus
12 and the needs of sponsors, regulators, and patients for transparent and consistent standards in
13 a broad range of fields.

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1 Efficient assessment of new medical devices requires significant collaboration between
2 the Food and Drug Administration (FDA) and manufacturers, scientists, and clinical researchers.
3 A critical component of this relationship is the FDA’s publication of detailed guidance
4 documents. These publications represent FDA's current approach to a given topic, yet are not
5 legally binding or developed as part of the formal federal rulemaking process. (1, 2) To date,
6 thousands of guidance documents have been published, providing transparency about
7 regulators’ expectations and priorities in regulatory approval processes to manufacturers in
8 both the pharmaceutical and medical device industries. (2) These guidance documents are
9 generally viewed as helpful for innovator firms. Indeed, a major shortcoming of the Center for
10 Devices and Radiological Health (CDRH) has been identified as “insufficient guidance for
11 industry,” (3) and industry groups regularly articulate “areas where guidance may currently be
12 lacking,” (4) a clear acknowledgment of the belief that more guidance is helpful and
13 appreciated.

14 Guidance documents themselves may cover specific product types (e.g. hearing aids),
15 regulatory processes (e.g. use of specific international standards), or broad areas of regulatory
16 concern that span many product types (e.g. cybersecurity for devices containing software).
17 Ideally, guidance documents support transparency and consistency in drug and medical device
18 regulation while providing opportunities for public engagement during the drafting process. In
19 this article, we consider the specific case of implantable breast prostheses as an avenue
20 towards understanding the essential role of FDA guidance documents in facilitating clinical
21 research and the introduction of safe and effective medical devices to patients.

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1 **The Regulatory History of Breast Prostheses**

2 Breast prostheses are annually implanted in hundreds of thousands of patients for
3 augmentation of breast size as well as in reconstructive surgeries following injuries or
4 mastectomies, supporting a \$1.2 billion industry (5, 6) and providing important improvements
5 in patients' quality of life. (7) Although breast prostheses have been on the market since the
6 1960s, the FDA only gained authority to regulate these devices through the 1976 Medical
7 Device Amendments to the Federal Food, Drug, and Cosmetic Act, which established the basic
8 risk-based regulatory framework for medical devices that remains in place today. In the 1980s,
9 breast prostheses were formally classified as high-risk devices, a distinction with implications
10 for the regulatory oversight of new product submissions as well as the financial commitment
11 from sponsors. For most high-risk medical devices, such as breast prostheses, the FDA requires
12 a premarket approval (PMA) application, which includes sections with information on products'
13 technical aspects, non-clinical laboratory studies, and clinical investigations. Relative to
14 applications for low or moderate-risk products, the PMA application is also costlier for
15 sponsors, who typically need to conduct clinical trials to support product approval.

16 In the case of breast prostheses, a 1989 study revealed that polyurethane foam, a
17 coating on some silicone gel-filled implants, degraded and released 2-toluene diamine, which
18 was known to cause cancer in animals when exposed to a high pH. (8) After the FDA requested
19 additional information about the safety and composition of the foam, the manufacturer
20 removed these implants from the market. Concerns around the safety of these prostheses
21 extended into the 1990s with lawsuits from thousands of women claiming injury from silicone
22 implants, but few studies were published assessing the safety and effectiveness of any

1 marketed product model. The FDA General and Plastic Surgery Devices Panel convened
2 multiple times to determine whether the PMA data was sufficient to establish that the silicone
3 gel-filled breast implants were safe and effective. In 1997, the National Academy of Medicine
4 performed an independent review of all past and ongoing scientific research regarding the
5 safety of silicone breast implants. (8)

6 The maelstrom surrounding breast prostheses represents an ideal context for public
7 discussion and medical and regulatory consensus distilled into comprehensive guidance
8 documents: the setting involves an important clinical need, combined with high public concern
9 about product safety, and a desire from manufacturers and regulators for a consistent and
10 transparent approach to assessing the biochemical, engineering, and clinical aspects of new
11 product submissions.

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13 **FDA Guidance Documents**

14 Many guidance documents detail the type of clinical evidence expected in order to
15 attain regulatory approval for new drugs and devices. They represent the FDA's current thinking
16 on a particular product, although, as noted above, they are not legally binding on sponsors or
17 the FDA. The FDA publishes such documents regularly and their full draft and revision history is
18 publicly available. To explore the impact of guidance documents on product research and
19 development, we identified all breast prosthesis approvals over the past 20 years from the
20 FDA's PMA database, (9) alongside all related final regulatory guidance documents published by
21 the CDRH over the same period of time. We also identified all published clinical studies
22 pertaining to breast prostheses. Figure 1 illustrates the growth of CDRH final guidance

1 documents since 1999 (1a) alongside the accumulation of those final guidance documents
2 specific to breast prostheses, new breast implant products, and publication of related clinical
3 studies (1b).

4 The first guidance document on breast prostheses was drafted in 1998 and finalized in
5 2001. It described recommendations regarding preclinical and clinical data, as well as labeling
6 information. This document was then revised in 2003 to provide new recommendations for
7 manufacturers surrounding the type and quantity of preclinical and scientific data that should
8 be submitted to determine device safety and effectiveness, with a focus on the clinical,
9 mechanical, and labeling sections of the guidance document. Following the publication of the
10 2003 guidance, another guidance was drafted in 2004 and finalized in 2006. The 2004 draft
11 provided new recommendations about mechanical testing, modes and causes of rupture,
12 clinical study information, post-approval requirements, and labeling. In 2006, this guidance
13 document was finalized to include updates to mechanical data, device explant analyses, core
14 study clinical data, and post-approval requirements. (9)

15 We find that the emergence of FDA guidance preceded the growth of scientific
16 publications around breast prostheses. Prior to the availability of the finalized 2006 guidance,
17 only a handful of studies had been published (0.30 +/- 0.57 papers/year published in the period
18 1987-2006.) Yet after 2006, published studies grew in number, variety and scope,
19 incorporating studies of devices from multiple manufacturers, prospective studies,
20 retrospective studies, and head-to-head comparisons (2.27 +/- 1.56 papers/year in the period
21 2007-2017, P=0.0017 for comparison to the prior period). Over the same period, six new
22 products received FDA approval, quadrupling the available options.

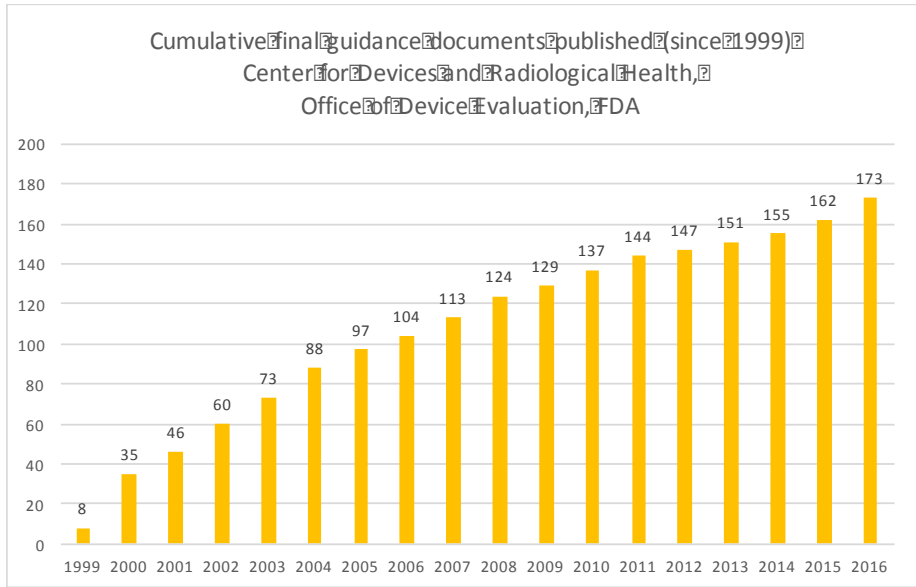
1 It is difficult to establish a causal relationship between the publication of regulatory
2 guidance and subsequent clinical studies and new product development. We recognize that a
3 limitation is the potential confounding variable that increased attention focused on a particular
4 device area due to clinical or safety concerns may drive an increase in both the number of
5 guidance documents published and innovation in the field. Still, the association between CDRH
6 guidance documents related to breast prostheses and subsequent growth in research and
7 innovation in these devices is compelling. This example illustrates the importance of supporting
8 FDA with sufficient resources to support guidance document drafting, revision, publication, and
9 updating to reflect evolving scientific consensus and the needs of sponsors, regulators, and
10 patients for transparent and consistent standards. Indeed, in recent statements regarding the
11 FDA’s budget, Commissioner Scott Gottlieb has highlighted that in the context of “advancing
12 modern drug and biological product manufacturing technologies,” additional resources would
13 be used to “lead stakeholders in the development of clear scientific standards, policy and
14 guidance.” Moreover, in the current political environment, where formal rulemaking by federal
15 agencies is becoming more difficult in health care and other settings, (10) the role of guidance
16 documents is likely to become increasingly important.

17 While the approval of a new medical technology is often viewed as a discrete event, it is
18 worth remembering that these approvals take place in a rich ecosystem of regulatory resources
19 and clinical research, facilitating learning and innovation over time. Ongoing efforts towards
20 streamlining medical product review should include additional resources for FDA to continue
21 developing focused, impactful guidance in areas of high clinical need.

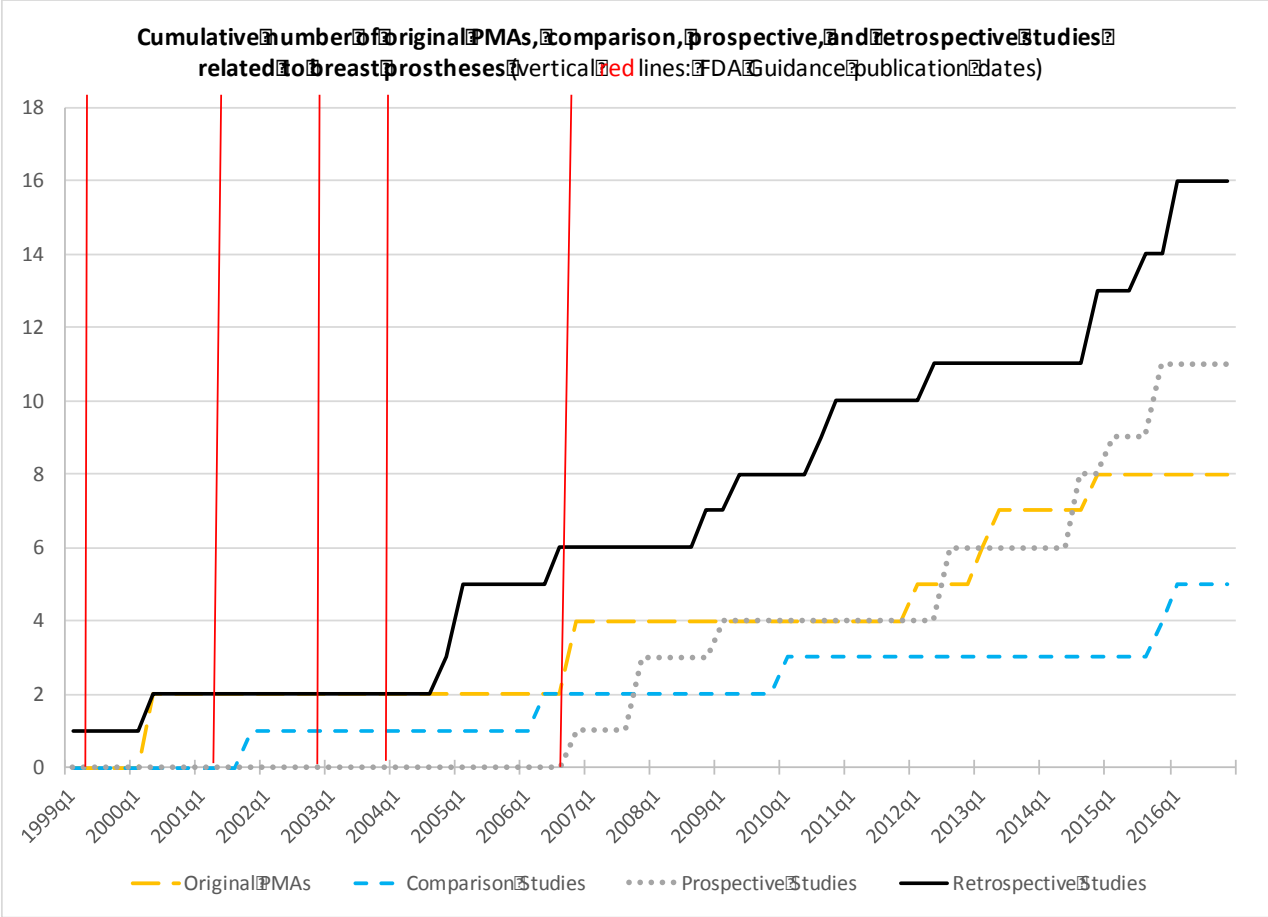
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2 **Figure 1a and 1b:** Publication of final Food and Drug Administration guidance documents
3 (Panel A) and the growth in scientific publications and regulatory submissions (Panel B) relative
4 to final guidance publication specific to breast prostheses.
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