The State of a Federal Regulatory Agency (FDA) under the Bush Administration

ASSESSMENT OF THE FDA BACKGROUNDER ON PLATINUM IN SILICONE BREAST IMPLANTS: IMPLICATIONS FOR PUBLIC HEALTH POLICY

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A recent report by the U.S. Food and Drug Administration reviewed the literature on the subject of platinum in silicone gel–filled breast implants. In this study the author evaluates the FDA report for scientific accuracy and impartiality, and provides relevant discussions on financial conflicts of interest, an Institute of Medicine report, and public health policy. The study suggests that the FDA used discredited scientific practices in compiling its report. Reports by regulatory agencies should be scientifically accurate, with no partiality to industry. The current policy of one-way information flow from the FDA directly to those being informed needs to be revised. Greater importance should be placed on studies in which authors have no financial conflicts of interest.

Millions of women in the United States alone have had breast implants placed for augmentation purposes, following mastectomy due to breast cancer, or for other reasons, such as chest wall deformities. Approximately 200,000 adverse event or reaction reports about breast implants have been submitted to the U.S. Food and Drug Administration (FDA) since 1985 (1). However, to date, there is no clear explanation for the symptoms and diseases reported by women with breast implants.

Medical-grade silicone is used as the gel in silicone breast implants, and as the encasing shell in both silicone and saline breast implants. Platinum (Pt) is a metal used in the manufacturing process to produce silicone breast implant gel material

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and silicone breast implant shells (2). Platinum may occur in the metal state as Pt(0) or in higher oxidation states, such as 2+ or 4+. Platinum in the metal state, or the zero oxidation state, is generally considered to be a nonreactive form. Platinum in all other oxidation states is considered to be reactive. Compounds that contain higher oxidation states of platinum have been shown to produce adverse health effects in humans (3–9).

Recently, the FDA published a report (10) that reviewed the literature on the subject of platinum in breast implants. As the FDA is charged with protecting the U.S. public health, it is often looked to as a source for accurate and impartial information. However, several instances over the past five years of drug recalls (11) after FDA approval, the mishandling of Plan B, the emergency contraceptive, application (12), and the overall growing politicization of the agency (11, 13), call into question the soundness of the scientific decisions that determine the FDA's review of drugs and medical devices. An assessment of the FDA report on platinum in breast implants is therefore warranted.

Detailed here is an evaluation of the FDA report for scientific accuracy and impartiality. Relevant discussions on financial conflicts of interest, an Institute of Medicine (IOM) report (2), and public health policy are also included. This study provides important information that will help clarify the state of knowledge concerning platinum in breast implants, so that the field continues to move forward.

THE CATALYST AND PLATINUM OXIDATION STATES

The FDA report states: "Platinum is a metal used as a catalyst" (all FDA statements quoted from 10). However, platinum is not "used as a catalyst" during the manufacture of the gel and shell components of silicone breast implants. Rather, platinum metal is one of the starting materials used to make a catalyst that is then used in the manufacture of silicone breast implant components. This is an important distinction: while platinum is present in the zero oxidation state in the metal form, this is not necessarily the form of platinum present in the catalyst. The above statement by the FDA implies that platinum occurs in silicone breast implants in the zero (nonreactive) oxidation state.

The FDA report further states that "studies have reported that the platinum in breast implants is in the zero oxidation (zero valence) state," and also quotes the IOM report (2) as reaching the same conclusion. However, in none of the studies (i.e., 14–17) cited as evidence in the FDA report (or in the IOM report) was a breast implant or breast explant actually analyzed for platinum oxidation states. In addition, all of the cited studies (14–17) contained at least one author from industry, or received industry support.

Only one published study (18) to date has analyzed breast implants for platinum oxidation states. The authors demonstrated that the gel of explanted

breast implants contained platinum in largely the 2+ and 4+ oxidation states. However, the FDA report dismisses this evidence as "very unlikely" and states that "based on the existing literature, FDA believes that the platinum contained in breast implants is in the zero oxidation state."

FINANCIAL CONFLICTS OF INTEREST

The FDA report also considers a review paper (19) on platinum in silicone breast implants. The review contained many non–peer-reviewed works as references, as well as internal company documents by manufacturers (which were also non–peer-reviewed) to substantiate scientific points. In addition, the paper contained inaccurate information. For example, the number of available samples in one of the reviewed studies (20) was misrepresented as 16 of 64, when in fact it was 16 of 35. Moreover, the author (Brook) of the review paper (19) divulged substantial financial conflicts of interest. In contrast, the authors of at least two studies cited above (18, 20) had no financial conflicts of interest. Authors' financial conflicts of interest and industry sponsorship have been associated with a greater likelihood of reporting findings favorable to industry compared with studies by authors with no such conflicts of interest, or research funded by other sources, or research not supported (21–27). Notwithstanding, the FDA report states that the "FDA concurs with Brook's conclusions."

PLATINUM AND ILLNESS IN WOMEN

The FDA report states that "FDA scientists reviewed the available studies from the medical literature on platinum and breast implants and did not find evidence that platinum present in silicone gel breast implants causes illness in women with breast implants." However, the reference cited (28) in the FDA report reviewed only one study (i.e., 29). This study (29) was, at the time of the review (28)—and remains today—the only scientific or medical publication that has addressed the subject of platinum in breast implants and illness in women. The study involved a case series of eight breast implant recipients, and supported the hypothesis that hexachloroplatinate (a compound that contains a higher oxidation state of platinum) was related to the symptoms these patients experienced.

A lack of evidence for platinum-related health problems in women with silicone breast implants is entirely different from evidence of no effect, and great care should be used in making this distinction. However, the FDA report suggests that appropriate studies have been conducted and were reviewed, when, in fact, if evidence is lacking for an association between platinum and health problems in women, it is because no studies have been conducted to investigate the possible association, and more research is needed.

PLATINUM FROM SILICONE IMPLANTS

The FDA report states: "Because small amounts of platinum remain in the product following manufacturing, concerns have been raised that platinum may enter the body, either by diffusing through the intact shell or through an implant rupture." However, since platinum remains in silicone breast implants following manufacturing, once a device is implanted, platinum has entered the body. Diffusion or rupture may be necessary for the distribution of platinum contained in the silicone gel, but no subsequent mechanism is necessary for platinum contact from the silicone envelopes.

The purpose of one study (20) reviewed in the FDA report was to document whether platinum was present as one moves outward from implant gel to implant envelopes to the tissue in direct contact with the implants in exposed women. However, the FDA report refers to this entire study as "seriously flawed" because control tissue samples were not used; in fact, a comparison with control tissue samples was not one of the intended, primary purposes of the study.

In addition, in reviewing another study (18) that made cross-study comparisons, the FDA report states that "the only appropriate comparison would have been with samples collected and analyzed concurrently." However, cross-study comparisons are commonly used, standard methods for exposure analysis and interpretation, and therefore entirely appropriate (e.g., 30–37).

INSTITUTE OF MEDICINE REPORT

The IOM report (2) is an often-quoted reference on the topic of platinum in silicone breast implants. According to the FDA report, the IOM "report provides an authoritative and unbiased review." In addition, the IOM report states that there was a "focus on evidence reported in the peer-reviewed, published scientific literature" (2, p. 16). However, with respect to the sections that address the amount of platinum in breast implants, the references cited in the IOM report consist almost exclusively (i.e., seven of nine references) of manufacturers' non–peer-reviewed company documents or personal communications by individuals employed by manufacturers (2, pp. 67–69).

Furthermore, the possible bias of the IOM report is illustrated by its assessment of a peer-reviewed journal article (38) that reported a value of approximately 4.5 μg/g platinum in silicone gel. As this value was higher than the data reported by manufacturers, the IOM report deemed the peer-reviewed publication (38) questionable, and states that "the higher measured value is confusing." Finally, the IOM report includes data that cover only up to part of 1999, and a number of peer-reviewed papers on the subject of platinum in breast implants have been published since the IOM report.

SUGGESTIONS

Bias toward industry has compromised the integrity of science in the United States (39), and this study suggests this effect is evident at the FDA in the field of medical devices. The FDA report on silicone breast implants represents information that the agency provided directly to the public. This study suggests that the current policy of one-way information flow from the FDA directly to those being informed should be revised.

The FDA currently relies heavily on unpublished results conducted and/or submitted by manufacturers, and on studies by financially conflicted authors, in making regulatory decisions. But scientific credibility is compromised when authors stand to gain financially from the results of a study, or when authors are associated with companies whose primary responsibility is to generate profits for shareholders. Regulatory agencies have a responsibility to the public to be scientifically accurate, and should have no partiality to industry. Public health decisions, therefore, should be informed by the best available evidence—scientific and medical research published in peer-reviewed journals by authors with no financial conflicts of interest. Greater importance should be placed on primary data, higher-quality studies, and studies by authors who have no financial conflicts of interest. Regulatory decisions should be made in a manner that best ensures that the public's health is adequately protected (40).

CONCLUSIONS

This study suggests that the FDA used discredited scientific practices in compiling its report on silicone breast implants. The same scrutiny applied to experimental papers (18, 20) authored by scientists with no financial conflicts of interest were not applied to a review article (19) written by a financially conflicted author. A fallacy of objectivity has been associated with the IOM report (2) on the amount of platinum in breast implants, and it is an out-dated reference for this subject. The current policy of one-way information flow from the FDA directly to those being informed needs to be revised. Reports by regulatory agencies should be scientifically accurate, with no partiality to industry. Greater importance should be placed on studies by authors who have no financial conflicts of interest.

Note — The author has no financial conflicts of interest, and has not consulted for breast implant manufacturers or for plaintiffs' attorneys. The author's interest in this subject is scientific and medical. Neither the author nor the Center for Research on Environmental Medicine has received any monies from breast implant manufacturers or from plaintiffs' attorneys.

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