DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

NOV 17 2006

Marlene Keeling, President
Chemically Associated Neurological Disorders
P.O. Box 682633
Houston, TX 77268-2633

Re: Citizen Petition - Docket Number 2006P-0151
Dated: April 6, 2006
Received: April 7, 2006

Dear Ms. Keeling:

This letter responds to your citizen petition (petition) dated April 6, 2006, submitted on behalf of Chemically Associated Neurological Disorders. You ask that the Food and Drug Administration (FDA) stay the approval of all premarket approval applications (PMAs) for silicone gel-filled breast implants for an indefinite time due to information you believe raises questions regarding the toxicity of platinum used in the implants.

DECISION SUMMARY

Your request that we stay the approval of all PMAs for silicone gel-filled breast implants for an indefinite time is denied. The agency has approved PMAs for these devices because the data submitted in support of each PMA, taken as a whole, provides reasonable assurance of the safety and effectiveness of the devices and, therefore, meets the statutory standard for approval. The Agency believes, based on existing scientific evidence, that the small amounts of platinum present in silicone gel do not pose a significant risk to women with silicone gel-filled breast implants. As described below, we believe that some of the studies you have referenced have serious scientific flaws (e.g., lack of concurrent controls and identification of oxidation states of platinum that are inconsistent with the known chemistry of platinum) that raise concerns about the validity of their results and conclusions.

OVERVIEW

Section I below sets forth the background regarding platinum. Section II sets forth the agency's review and analysis of your petition. Section III sets forth the agency's summary conclusion.

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DISCUSSION

I. BACKGROUND

FDA is aware that, for several years, questions have been raised regarding the safety of platinum compounds used in the manufacture of silicone gel and elastomer. In addition to having sponsors provide toxicology studies as part of their biocompatibility testing, FDA recommends that sponsors provide detailed information on the identity and quantity of breast implant constituents, including platinum, that may bleed from intact devices. FDA also monitors the scientific and medical literature to keep apprised of new findings on gel bleed and the potential toxicity of platinum.

As a result of our interest in this issue, FDA commissioned the Institute of Medicine (IOM) to evaluate the safety of platinum catalysts used in the manufacture of silicone breast implants. The report, "Safety of Silicone Breast Implants," published in 2000, included a comprehensive and authoritative review of the literature regarding the chemistry and toxicology of platinum in silicone gel breast implants, including reviews of two of the articles discussed or referenced in your petition (Lykissa, et al., 1997 and Harbut and Churchill, 1999). The IOM Committee concluded, "...that a review of the toxicology studies of silicones and other substances known to be in breast implants does not provide a basis for health concerns" [p.10]. Specifically with regard to platinum catalysts, the Committee concluded, "The evidence currently available suggests that platinum is present only in the zero valence elemental state. Evidence does not suggest there are high concentrations in implants, significant diffusion of platinum out of implants, or platinum toxicity in humans" [p.3].

II. ANALYSIS

Below are responses to each bulleted statement of grounds in your petition.

A. Response to the first bulleted statement of grounds

Your petition states that Maharaj "...found significant platinum levels in the connective tissue of breast implanted women." To be more specific, very small amounts of platinum (between 3 and 272 parts per billion) were reported in 15 capsular tissue samples analyzed by mass spectrometry. However, FDA believes that the study is seriously flawed because control tissue samples from women without breast implants were not included for comparison. Therefore, it is not possible to determine if the amounts of platinum reportedly found in the tissues from implanted women are higher than amounts that might be found in tissues of women who never had breast implants.

You include the statement from the Maharaj article that, "Platinum most likely occurs in implant material as hexavalent platinum (Pt) compounds, along with other ionized forms of Pt;.. Although the concentration of Pt+6 is unknown, given the high toxicity and biological activity of ionized forms of platinum, any amount may be too much." The Maharaj study did not identify any particular molecular or ionic form of platinum in the tissue samples. Maharaj's statement

refers to an earlier study by Lykissa, et al. (1997), who reported finding that platinum leaked from intact explanted breast implants into a lipid rich medium. However, the methodology used by Lykissa, et al. could not be used to identify the form of platinum and no claims were made that Pt+6 or other ionic forms were detected. Lykissa, et al. state, "Our ICP-MS analyses do not allow direct determination of whether platinum in implant gels is present as inorganic metal as opposed to organic or silicone-based complexes." The IOM report stated, "Platinum is present in small amounts in implants...Reports that this platinum is in the form of platinate (Lykissa, et al., 1997) are unconfirmed" [p.108]. In conclusion, FDA believes there are serious doubts about the validity of the results and conclusions in the Maharaj article.

B. Response to the second bulleted statement of grounds

FDA has serious questions about the statements presented in your petition that are based on the recent publication by Lykissa and Maharaj in Analytical Chemistry (2006). Your petition states that the authors concluded that "Women exposed to silicone breast implants had higher Pt levels by approximately 60 to >1700x for urine, 14x for nails, and 100x for breast milk samples, than individuals with no known Pt exposure." However, the report by Lykissa and Maharaj states, "Mean Pt concentration in urine samples from women exposed to silicone breast implants and that of control subjects did not show a statistically significant difference" [p.2930]. The comparison for urinary levels shown in your petition (and also made in the Lykissa and Maharaj article, in contradiction to their statement quoted above) is based on historical literature data, and not on the results for controls obtained by Lykissa and Maharaj in their own study. FDA believes that the only appropriate comparison is with the data obtained concurrently, since the subject population, sample collection and processing, and analytical methodology were most likely different in the earlier referenced studies. Furthermore, the Lykissa and Maharaj study did not include control samples from women who never had implants for comparison with the platinum levels obtained for the hair, nail, and breast milk samples from women who were exposed to breast implants. As with the urine analyses, only samples from control subjects collected and analyzed concurrently with the test samples are appropriate for comparison.

Therefore, the data in the Lykissa and Maharaj article actually show that platinum levels in urine from women exposed to silicone breast implants (determined to be in the parts per million range based on urinary creatinine) are no higher than levels in control urine samples, and the significance of results for hair, nail, and breast milk analyses (determined to be in the parts per billion range) can not be established.

FDA is also concerned about the validity of the statement made in the article that, "Pt in explanted silicone breast implant gel, whole blood, urine, brain tissue, and breast milk samples from women exposed to silicone breast implants occurred mainly in reactive forms ... Silicone breast implants are the most likely source of the elevated total Pt levels and the reactive forms of Pt in women exposed to these devices" [p.2933]. The authors reported results for the various charged forms of platinum (i.e., oxidation states) in seven blood samples, one urine sample, and one sample of brain tissue from women with implants; breast milk was not analyzed. The gel isolated from the explanted devices was also analyzed. All seven blood samples reportedly contained oxidation states +2 and +4; Pt(0) was present in two samples, and Pt(+6) in four

samples. The sample of brain tissue reportedly contained Pt in oxidation states 0, +2, and +4, whereas oxidation states +2, +4, and +6 were found in the urine sample. One or more of all the theoretically possible oxidation sates of platinum (Pt(0) through Pt(+6)) were reportedly present in the explanted gel material.

Although platinum is commonly found in the +2 and +4 oxidation states, FDA questions the finding of +1 (n=2), +3 (n=2), +5 (n=2), and +6 (n=5) in the gel samples, as well as Pt(+6) in the blood (n=4) and urine samples. Lykissa and Maharaj provide no evidence from the scientific literature that these oxidation states are commonly found in nature or are produced under other than extreme laboratory conditions. To FDA's knowledge, there is no reason to believe that these forms of platinum would be introduced during implant manufacture. Their findings, if correct, would be extraordinary and would require additional work by independent researchers to establish their credibility.

Finally, FDA takes issue with the statement made by Lykissa that you cite in the fourth bulleted statement of grounds, "Our current publication in Analytical Chemistry (2006) finally arrives with ample evidence for the cause of ill health effects of these devices. The platinum catalyst that has been incorporated into the silicone gel component of the implants is being released from the depolymerized silicone gel and in the ionized form it is free to attack the human tissues, including the nervous system." In view of our comments discussed above and in other sections of this response, FDA believes this statement is speculation and is not supported by sound scientific evidence.

C. Response to the third bulleted statement of grounds

This abstract by Maharaj and Lykissa presented at the American Chemical Society meeting in 2005 describes results of mass spectrometric analysis of platinum in the urine of women exposed to silicone gel- or saline-filled breast implants and in urine samples from children conceived before or after their mothers received their implants. The abstract states, "Mean Pt concentration in the urine samples of women exposed to silicone breast implants was higher ...than in that of the general population. Mean platinum concentration in urine samples of children conceived after their mothers were implanted with silicone breast implants was higher than in children conceived before their mothers were implanted...and higher than that in the general population. Women exposed to saline breast implants did not have elevated urinary Pt levels" [Exhibit C]. The reported levels were small, in the parts per billion range.

FDA considers these to be preliminary results that require independent confirmation. The technical and analytical details are scant and additional information is needed to determine if the experimental design and data analysis are valid. For example, it is not clear whether the platinum levels in the women's urine samples were compared with concurrent samples from women who never had breast implants, or whether the comparisons were made with historical controls, which, as noted above, FDA believes is inappropriate. In addition, to be consistent with standard clinical laboratory practice, the platinum levels should have been based on urinary creatinine to obtain more accurate values for comparison, not on volume of urine. The authors normalized the values using creatinine in their 2006 Analytical Chemistry article [Table 2,

p.2929], and when this method was used, there was no significant difference between urinary platinum levels in women with or without breast implants [p.2930].

D. Response to the fourth bulleted statement of grounds

Your petition is highly critical of the recent review by Brook, "Platinum in silicone breast implants." Dr. Lykissa disclaims Brook's review because it contains no original research; however the intent of the article is not to provide new research findings, but rather to provide an overview of the published scientific literature on the subject, as well as information available from other sources outside the realm of peer-reviewed scientific literature. The journal editor noted that, "On receipt of this unsolicited review, the Editor-in-Chief selected two highly qualified referees, both well known for their robust and impartial scientific work on silicone breast implants, who both submitted extensive, constructive but critical reports on the manuscript. ...the Editor-in-Chief believes that the published version is a scientifically valid, academically sound review of the subject."

In any case, FDA did not rely on Brook's review to evaluate your petition. Rather, FDA's own expert chemists, biologists, engineers and materials scientists provided an independent evaluation of the material you submitted to support your request. FDA also continues to use the IOM report as an important scientific resource to evaluate the older literature because the report provides an authoritative, thorough and unbiased critique of the pertinent issues related to platinum chemistry, biology, and health effects known at that time.

E. Response to the fifth bulleted item

You expressed concerns about Inamed's gel bleed testing for platinum presented at the 2005 panel meeting. After that panel meeting, Inamed provided new gel bleed testing using a new methodology designed to mimic the environment of the implant in the body so that they could more reliably predict the gel bleed from implanted devices. FDA believed the new testing was adequate to identify and quantify the types and rates of gel bleed constituents, including platinum.

FDA takes issue with Dr. Lykissa's statement in the 2006 Analytical Chemistry article suggesting that platinates are used in the manufacture of silicone gels for breast implants, and that the chemical reactions to produce the silicone shells are "...catalyzed with ionized Pt" [p.2933]. The IOM committee examined the issue of the catalysts and reported that the scientific literature indicates that platinum in the catalysts is in the zero oxidation state [p.3]. Dr. Lykissa also states, "Depending on the amount of ionized Pt that is liberated by the degradation process, proteins may become vulnerable to denaturation" [p.2933]. Because there are no data to support it, FDA considers this statement to be speculation rather than a demonstrated scientific fact.

F. Response to the sixth bulleted item

This item consists of data sheets for platinum analyses carried out by Dr. Lykissa's laboratory on samples from two women who had third generation gel-filled implants and the son of one of

these subjects. The samples include urine and breast secretions from both women, a sample of fat tissue from one, and urine results for the child, who was born after his mother had received her implants. Results include levels of elemental platinum (Pt(0)) and various oxidation states. The analytical method appears to be the same as that used in the 2006 Lykissa and Maharaj article discussed in item 2, above. For item 6, comparable analyses for controls (women who never received silicone breast implants, and urine from children whose mothers never had implants) are not included. Therefore, it is not possible to determine if the subjects had platinum levels higher than the general population of similar subjects, and the meaning of the findings is unclear. The same criticisms related to the chemistry of platinum oxidation states discussed in item 2 also pertain to this study.

G. Response to the seventh bulleted item

Dr. Michael Harbut is quoted as follows, "I have treated over 1,000 women with breast implants and have regularly seen the diseases caused by platinum salt exposures. As I published in 1999, women with exposure to platinum salts via their implants commonly present with shortness of breath, asthma, itching, rhinitis, memory loss, gastrointestinal disturbances, sometimes pulmonary fibrosis and sometimes COPD, among other, less common presentations." Regarding the 1999 publication, the IOM report states, "These authors speculated that the respiratory signs and symptoms were the results of exposure to hexachloroplatinate in their implants. No evidence for this was reported. Conclusions regarding platinum toxicity in women with breast implants should await evaluations that positively relate platinum to symptomatology... Absent these tests, diagnoses of platinum toxicity in women are speculative only" [p.109]. Because Harbut has not reported evidence that hexachloroplatinate is present in women's implants or biological samples, FDA believes that his claim that diseases in women with silicone implants are caused by platinum salt exposures remains speculation.

H. Response to the eighth bulleted statement of grounds

The study by Miller and Prihoda includes approximately 66 women who had breast implants. Of these subjects, 68% reported that their implants had ruptured and 78% had one or both implants removed. The report concluded that the women who had breast implants were more likely to have multiple chemical intolerances than the control group, based on responses to a validated questionnaire. However, the study does not include information on the types of implants (age, manufacturer, or gel- vs. saline-filled) or how long they had been implanted. In addition, it is not clear that the patient population enrolled in this study was an unbiased sample since subjects were recruited through advertisements in patient group newsletters and by word-of-mouth.

The study was not designed to determine, and the authors make no claims of, an association or causal connection between any of the multiple chemical intolerances and platinum or silicones. In addition, the results indicate that removal of the implants did not consistently lead to an improvement in symptoms. In this study, 9% reported their health status as greatly improved, but 24% reported it had greatly worsened after the implants were removed. The authors do not discuss this point, but it raises doubts that the conditions reported by the women were related to their breast implants. FDA believes this study does not provide useful information on the effects

of platinum or any other breast implant constituents on the health status of women who have or had silicone breast implants.

III. CONCLUSION

FDA has reviewed your petition and other relevant data and information available to the agency. For the reasons discussed above, your request that we indefinitely stay approval of all silicone gel-filled breast implant PMAs is denied.

Gel bleed testing in the approved Mentor and Inamed PMAs has shown that over 99% of the platinum in these devices stays within the implant. Based on FDA's review of the gel bleed testing, the published literature on this topic, as well as the biocompatibility testing and clinical data on the device, FDA has concluded that the low concentration of platinum contained in breast implants is in the zero oxidation state, or the state associated with the lowest toxicity, and, thus, does not pose a significant risk to women with silicone gel-filled breast implants.

FDA appreciates your continued interest in the safety of silicone breast implants. FDA takes women's special health issues very seriously, and maintains an active interest in the issue of platinum toxicity. FDA will continue to review the literature on breast implant related issues, including platinum, as part of our continuing oversight of the safety of breast implants.

If you have any questions about this response, please contact Myrna Hanna of our Regulations Staff at (240) 276-2347.

Sincerely yours,

Linda S. Kahan

Linda S. Kahan
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Center for Devices and Radiological Health