DEPARTMENT OF HEALTH & HUMAN SERVICES

EXHIBIT O

Food and Drug Administration
Rockville MD 20857

MAR 30 2001

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

Dear Ms. Keeling:

This letter is in response to your petition (Docket Number 00P-1607/CP-1) received by FDA on November 3, 2000 and filed on November 7, 2000. Your petition requested that FDA revoke the implantation of silicone gel-filled breast implants for any reason, and that remaining inventories of these devices in the United States be destroyed. Your petition also requested, upon confirmation of other independent research, that FDA issue a public health alert related to breast feeding or pregnancy, and to provide advice regarding breast implant removal. Your petition is based on concerns regarding release of residual platinum used as a catalyst in the manufacture of silicone breast implants.

Statement

For several years FDA has been interested in the safety of platinum compounds used to prepare silicone gel and elastomer. As a result, FDA asked the Institute of Medicine (IOM) to evaluate the safety of platinum catalysts used in the manufacture of silicone breast implants. Their recently published report, "Safety of Silicone Breast Implants", includes a comprehensive and authoritative review of the chemistry and toxicology of silicones and platinum. 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 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]. Furthermore, regarding clinical symptoms attributed to platinum salts, the report states, "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 with implants are speculative only" [p. 109].

Action

FDA has carefully reviewed your petition, along with additional data obtained from Dr. Lykissa. Although some new preliminary information was provided, FDA believes the IOM committee's conclusions regarding the lack of toxicity of platinum catalysts used to prepare silicone gel-filled breast implants are valid. FDA, therefore, is denying your

petition. Below is a more detailed discussion of the reasons for this action. The responses correspond to the heading numbers in your petition.

Response to item 1. FDA is aware that small amounts of residual platinum (parts per million) may be present in breast implants [IOM report, p. 67]. However, organoplatinum compounds, not hexachloroplatinate, are the catalysts that have been used to prepare silicones [IOM report, p. 67]. Although hexachloroplatinate is used to synthesize these organoplatinum compounds, there is insufficient experimental evidence for the presence of hexachloroplatinate in silicone gel or elastomer. The 1997 publication by Lykissa et al., to which you refer, did not identify hexachloroplatinate or any particular molecular or ionic form of platinum. Regarding this study, the IOM report states, "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].

Response to item 2. At our request, Dr. Lykissa provided additional unpublished information from his study on leakage of platinum from explanted breast implants. Although the data are suggestive that ionic platinum in various oxidation states may be present, neither hexachloroplatinate nor other platinum salts were identified. FDA believes that Dr. Lykissa's results are preliminary. They do not conclusively identify the molecular form of platinum nor do they establish that, if present, the reported ionic forms of platinum cause hypersensitivity or other toxic reactions in the amounts that may leak from breast implants (nanograms per month). No evidence was presented to establish an association or causal connection between clinical symptoms in the women in this study and platinum that might have leaked from their implants.

The IOM committee also reviewed the potential toxicity of silicon in breast-fed infants of mothers with breast implants. Their review was not limited to the study by Semple et al. to which you refer. Their report states, "... there is ample evidence that infants breast-fed by mothers with silicone breast implants receive no higher silicon intakes than infants breast-fed by mothers without breast implants. Infants receiving cows' milk or commercial infant formula feedings are likely to have higher silicon intakes than breast-fed infants. Evidence that any likely exposure to silicone or silicon has effects on infant health is lacking." [p. 252]. FDA concurs with this statement.

Response to items 3, 4, 6, and 7. FDA agrees that hexachloroplatinate and certain other chemically related platinum salts can cause allergic reactions in sensitized individuals. However, experimental evidence is lacking to support the claim that hexachloroplatinate is present in breast implants. Furthermore, the supplier of the platinum catalyst used to manufacture breast implants, and scientists who have studied the chemistry of these catalysts, have recently assured FDA that chloroplatinic acid is consumed during the formation of these catalysts and is not present in the materials used to produce the implants.

It is important to note that the chemical form of platinum is an important factor in its toxicity. Platinum in hexachloroplatinate has a valence of +4. The organoplatinum catalysts contain platinum in the zero valence state, and do not contain chloride. The IOM report states, "If the platinum in breast implants is in the zero valence form in the final cured state as reported by Stein et al (1999), and if it is in microgram quantities as is usually added to gel (Lane et la, 1998), as the current evidence suggests, then a biologically plausible rationale for platinum related health problems in women with silicone breast implants does not presently exist." [pp. 109-110]. FDA concurs with this statement.

FDA is aware that a condition referred to as "platinosis" may occur in refinery workers exposed to hexachloroplatinate or chemically similar platinum salts. However, a relationship between clinical effects of respiratory or dermal occupational exposure to hexachloroplatinate and potential effects in women who may be exposed to small amounts of platinum catalysts in breast implants has not been established. With regard to toxicity of platinum catalysts, the IOM report states, "Very little platinum, microgram quantities, is present in breast implants, most investigators believe it to be in the zero valence state, and it likely diffuses through the shell at least over a considerable period of time. Evidence for systemic disease at such exposures is lacking." [pp. 112-113]. FDA concurs with this statement.

Item 7 also mentions effects of elemental platinum. FDA believes that true allergic reactions to elemental platinum are rare and not representative of any group with silicone-containing implants. On this issue, the IOM report states, "Inhalation of complex salts, but not elemental platinum, can cause progressive allergic and asthmatic reactions." [p. 108]. FDA concurs with this statement.

Response to item 5. FDA believes that the statements in your petition regarding the study by Potter et al. are inaccurate. Their research did not establish "... that platinic chloride is a water-soluble form of the metal that is used as the catalyst in medical silicone gels and elastomers." Nor did their research establish "... that any soluble platinum leaching from an implant would be expected to distribute in the circulation as a chloroplatinate." Potter et al. did not study platinum catalysts nor did they attempt to detect chloroplatinate or other forms of platinum in the silicones they used or in the mice they studied. Potter et al. did not claim that platinum in any form was responsible for effects they observed in their study.

Response to items 8, 9, and 10. The IOM committee also provided an overview on the toxicology of silicones [IOM report, Chapter 4]. The chemicals studied included low molecular weight silicones and the silicone distillate discussed in your petition. Their report concludes, "... no significant toxicity has been uncovered by studies of individual compounds found in breast implants. Toxicology studies have examined carcinogenic, reproductive, mutagenic, teratologic, immunotoxic, and local and general toxic and organ effects by exposure routes that are varied and range to very high dose levels. Even challenges by doses that are many orders of magnitude higher than could be achieved on

a relative-weight basis in women with silicone breast implants is reassuring." [p.112]. FDA concurs with this statement.

With regard to the studies of the silicone distillate by Kala, et al. and Liberman, et al. discussed in your petition, the IOM report states, "It is not clear what relevance these studies have to women with silicone breast implants, since test article doses were given that were orders of magnitude greater than possible from breast implants, and LD_{50}s in these ranges have historically been considered indicative of lack of toxicity..."[p. 100]. The committee also was concerned about the appropriateness of the test material. Their report states, "It was not clear to the committee why a distillate, instead of an extract or simply reference compounds, was used, since the possibility that some of these compounds were created during distillation once again raises the question of relevance for women with silicone breast implants." [p. 100]. FDA concurs with these statements.

Response to item 11. Your petition suggests that platinum present in breast implants plays a role in health effects reported in several cited articles. The IOM committee included these articles as part of their review and concluded that there is insufficient evidence that breast implants, including residual platinum catalysts, are responsible for any observed clinical symptomatology. For example, in reference to the 1999 study by Härbut and Churchill on asthma in women with silicone breast implants, the report states, "These authors speculated that the respiratory signs and symptoms were the result of exposure to hexachloroplatinate in their implants. No evidence for this was reported." [p. 109]. With regard to esophageal disease in children, including the studies by Levine et al., "The committee can not imagine, and finds no evidence for, any immune mechanism associated with breast milk that would produce esophageal or immune-autoimmune changes a decade after breast feeding... No biologically plausible mechanism for an immune or silicone effect in breast milk associated with esophageal changes is apparent to the committee or has been suggested by others... a well-designed epidemiological study provides no support for an association of esophageal disease in children with silicone breast implants in their mothers" [p. 260]. FDA concurs with these statements.

Response to item 12. The studies of Campbell et al. and Salvato did not demonstrate that reduced numbers of natural killer (NK) cells in their patient populations were attributable to platinum salts. Although Dr. Salvato's results were not available to the IOM committee, her results are consistent with decreases in cell numbers found in the earlier studies that were included in the IOM committee's review. With regard to NK cells the IOM report states, "...there is no clear evidence that changes in NK-cell activity have functional effects or explain the signs and symptoms that characterize women with silicone breast implants who have chronic and unremitting complaints." FDA concurs with this statement.

Effects on NK cells have been attributed to several different causes, although adverse immunologic effects of these changes have not been demonstrated. The IOM report states, "... previous studies have demonstrated that NK-cell activity can be altered by stress, sleep loss, and various medications... among otherwise healthy subjects" [p. 184]. Also, "... geographic location, gender, age, and even occupation of control populations

can affect NK-cell activity and that low NK-cell activity is observed in chronic fatigue syndrome... without a consistent correlation with immune defects having been discovered." [p. 184].

In their review of "Neurologic Disease and Its Association with Silicone Breast Implants" [chapter 10], the IOM committee reported that, "... the evidence for a general neurologic disease or syndrome caused by, or associated with, silicone breast implants is insufficient or flawed." [p. 247].

FDA believes that statements in your petition suggesting that changes in NK-cell activity indicate neurologic or immunologic disease in women with silicone breast implants are inconsistent with the conclusions reached by the IOM committee.

Response to item 13. FDA's position regarding the molecular form of platinum catalysts in silicone breast implants and their lack of toxicity was discussed in the information above. With regard to a "...novel illness triggered by silicone gel-filled devices," mentioned in your petition, the IOM report states, "... there does not appear to be even suggestive evidence of a novel syndrome in women with breast implants. In fact, epidemiological evidence suggests that there is no novel syndrome." [p. 11]. FDA concurs with this statement. Although the IOM committee did not review Dr. Brawer's recent study, Dr. Brawer discussed his results with FDA at a meeting in September, 2000. FDA considers the results preliminary, and believes the IOM report's conclusions remain valid.

Other information. In the introductory statement, you request that FDA issue a public health alert regarding breast-feeding or pregnancy to avoid possible genotoxic effects. The "ENVIRONMENTAL IMPACT" statement also refers to potential toxicity of breast implant constituents, including "hypersensitizing platinum," that "...are passed in the placenta or in breast milk." FDA believes the IOM committee was thorough in reviewing the available information on health effects in children. Its conclusions on this important issue were clear and emphatic. Their report states, "The committee finds no evidence of elevated silicone in breast milk or any other substance that would be deleterious to infants; the committee strongly concludes that all mothers with implants should attempt breast feeding." [p. 11]. Also, "The committee concludes that evidence for health effects in children related to maternal breast implants is insufficient or flawed." [p. 11]. FDA concurs with these statements.

Your petition also requested that FDA provide advice related to breast implant removal. FDA has provided information for women on this topic in two documents available on the Center for Devices and Radiological Health internet site, www.fda.gov/cdrh/breastimplants. Both documents, "Breast Implants: An Information Update 2000" [pp. 2 and 23] and "Breast Implant Risks", inform women who have received or are considering breast implants about the potential need for additional surgeries.

Conclusion:

FDA appreciates your interest in the safety of silicone breast implants. The Agency takes women's special health issues very seriously, and has maintained an active interest in the issue of platinum toxicity for several years. Although your petition has been denied, FDA will continue to evaluate results of new studies, and will adjust our level of concern accordingly. If you have any questions on the information given above, please contact Dr. John Langone at 301-443-2911.

Sincerely yours,

Linda S. Kahan

Linda S. Kahan
Deputy Director for Regulations and Policy
Center for Devices and Radiological Health