VII. CONCLUSIONS

These studies were conducted for McGhan Medical Corporation by

to determine the potential of Diaphragm Valve and Plug Assembly to compromise the immune system. In female B6C3F1 mice implanted with Diaphragm Valve and Plug Assembly Test Article for 28 days, no biologically significant effects were observed on standard toxicological parameters, including absolute spleen weight, thymus weight, thymus histopathology, leukocyte number and leukocyte differentials.

With the exception of the natural killer cell response, exposure to the Diaphragm Valve and Plug Assembly did not affect immune parameters when evaluated with an extensive panel of immune function assays. While alterations in the natural killer cell response were observed, it can not be determined from these studies if the effects on natural killer cell activity were due to the physical size and number of the implants administered or if the effects were due to the silicone elastomer material composing the Diaphragm Valve and Plug Assembly. B cells, T cells, T cell subsets, the antibody-forming cell (AFC) response and the mixed leukocyte response (MLR) were not affected at any dose level of Diaphragm Valve and Plug Assembly Test Article exposure.

The results from this comprehensive immunotoxicological evaluation demonstrate that, under the experimental conditions used, exposure to Diaphragm Valve and Plug Assembly does not adversely affect the functional ability of the immune system, with the possible exception of natural killer cells. The physical size and the number of implants used in this study may have contributed to the effects observed with the natural killer cell activity.

VIII. REFERENCES

1 Luster, M.I., Portier, C., Pait, D.G., Rosenthal, R.J., Germolec, D.R., Comment, C.E., Corsini, E., Blaylock, B.L., Pollock, P., Kouchi, Y., Craig, W., White, K.L., Jr. and Munson, A.E. 1993. Risk Assessment in Immunotoxicology: II. Relationship between Immune and Host Resistance Tests. *Fundam. Appl. Toxicol.* 21:71-82.

2 Bradley, S.G., Munson, A.E., McCay, J.A., Brown, R.D., Musgrove, D.L., Wilson, S., Stern, M., Luster, M.I. and White, K.L., Jr. 1994. Subcronic 10 day immunotoxicity of polydimethylsiloxan (silicone) fluid, gel and elastomer and polyurethane disks in female B6C3F1 mice. *Drug and Chem. Toxicol.* 17(3):175-220.

3 Bradley, S.G., White, K.L., Jr., McCay, J.A., Brown, R.D., Musgrove, D.L., Wilson, S., Stern, M., Luster, M.I. and Munson, A.E. 1994. Immunotoxicity of 180 day exposure to polydimethylsiloxan (silicone) fluid, gel and elastomer and polyurethane disks in female B6C3F1 mice. *Drug and Chem. Toxicol.* 17(3):221-269.

4 Jerne, N.K., Henry, C., Nordin, A.A., Fuh, H., Koros, M.C. and Lefkovits, I. 1974. Plaque-forming cells: Methodology and theory. *Transpl. Rev.* 18:130-191.

5 Luster, M.I., Munson, A.E., Thomas, P., Holsapple, M.P., Fenters, J., White, K.L., Jr., Lauer, L.D. and Dean, J.H. 1988. Development of a testing battery to assess chemical-induced immunotoxicity. *Fund. Appl. Toxicol.* 10:2-19.

6 Bartlett, M.S. 1937. Sub-sampling for attributes. *J. Roy. Stat. Soc. Suppl.* 4:131-135.

7 Kruskall W.H. and Wallis, W.A. 1952. Use of ranks in one-criterion variance analysis. *J. Amer. Stat. Assoc.* 47:583-621.

8 Dunnett, C.W. 1955. A multiple comparison procedure for comparing several treatments with a control. *J. Amer. Stat. Assoc.* 50:1096-1121.

9 Wilson, K.V. 1956. A distribution free test of analysis of variance hypothesis. *Psychol. Bull.*, 53:96-101.

10 Gross, A.J. and Clark, V.A. 1975. Gehan-Wilcoxon Test. In *Survival Distribution: Reliability Applications in Biomedical Sciences* (A.J. Gross and V.A. Clark, eds.). John Wiley & Sons, New York, p. 120-123.

11 Hollander, M. and Wolfe, D.A. 1975. Jonckheere's Test: Non-Parametric Statistics Methods (M. Hollander and D.A. Wolfe, eds.). John Wiley & Sons, New York, p. 124-129.

12 Sokal, R.R. and Rohlf, F.J. 1981. *Biometry*. Freeman, San Francisco, p. 226-231.