December 30, 1998

Mr. Daniel White
Vice President of Sales and Marketing
Advanced UroScience, Inc.
1290 Hammond Road
St. Paul, MN 55110-5367

Dear Mr. White:

I have had the opportunity to review the radiographs of the patients involved in the ISD injection protocol. The findings are, to my mind most interesting, as well as reassuring. The radiographs provide us with some interesting insight into the behavior of bulking agents injected into the urethra. Some of these findings I suspect would be generic to any agent and others would be unique to the Advanced UroScience product.

The most interesting finding observed in your product is that it shows no signs of migration between the twelve, eighteen and twenty four month intervals. This is in marked contrast to what has been observed with the injectable Teflon® product. In no instance, when I compared the twelve-month films with the subsequent follow up periods did I see any evidence of delayed migration or local dispersal of the material. The films were virtually superimposable. There was no evidence of local diffusion of the material over time.

Although I saw no evidence of material migrating over the time interval between the initial and the follow up films there is clearly some dispersion of the beads at the time of initial injection. This comes as no surprise and would be expected with any viscous injectable agent. I suspect we would see the same findings with Contigen® if the agent were radio-opaque. These findings would probably also be recognized with MRI's obtained after the injection of fat except for the ubiquitous nature of the material in most patients with ISD.

It appears that if the operating surgeon got the injection needle in the surgical plane between the lamina propria of the urethra and the muscularis the material was very locally confined. Periurethral extension into surrounding lymphatics and soft tissue was minimal. If, however, the material was injected deeper either into the muscle or periurethrally (usually manifested by a more diffuse local injection pattern) there did appear to be some local extension of the material. The general pattern suggested either local extension along tissue planes or local endoluminal extension. I cannot clearly state whether this was extension in lymphatics or local veins. The pattern looked very similar to the picture one sees after injecting a liquid iodinated contrast agent into the urethra

when there has been some disruption of the endothelial lining. There was, however, a difference. Unlike a liquid contrast agent that is miscible and has basically the same viscosity of blood or lymph fluid and can therefore travel to any part of the body, your agent appears to travel only a short distance. (Possibly due to the loss of the suspension medium versus thrombosis of the vein or lymphatic channel). I could see no evidence of gradual migration of the material with deposition of beads in the lymph nodes. In no instance did I see evidence of spread beyond the local confines of the pelvis. The material should not represent any threat to patient safety when within those confines.

These findings suggest to me that there is no danger of this material "metastasizing". I suspect that if you took radiographs immediately after the injection of the bulking agent the films would look very similar to the one year follow up films.

You have a very exciting product. Both my patients and I look forward to the time when this agent becomes available to the general public.

Sincerely,

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