

**MEMORANDUM**  
P020012

**SUBJECT:** Preclinical Review

**DEVICE:** Artecoll PMMA/Collagen Implant, P020012

**SPONSOR:** ARTES MEDICAL, INC.  
4660 La Jolla Village Drive, Suite 825  
San Diego, CA. 92122 USA

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**INDICATIONS FOR USE:**

Artecoll is indicated for the correction of contour deficiencies of soft tissue.

**Product Summary:**

Artecoll is a suspension of polymethylmethacrylate (PMMA) microspheres suspended in a bovine collagen solution containing phosphate buffer, sodium chloride, lidocaine-HCl and distilled water. The product is supplied in a four pack of sterile 0.5 ml pre-filled syringes.

**Preclinical Studies:**

While there is no FDA-approved device using the microsphere form of polymethylmethacrylate (PMMA) polymer, there is a long history of PMMA use in medical devices. In support of the safety and biocompatibility of Artecoll, the sponsor submitted the following preclinical studies in Volume 10 of the original PMA application.

Final Product Bench testing

- ?? *Extrusion force* – The plunger force required to expel 0.5 ml of Artecoll through a 27 gauge needle from a standard 1.0 ml syringe was determined. The average force for 3 lots of product was 3.1 lbs. Based on published literature that suggests that the estimated maximum lateral finger/thumb forces for men and women are 23.2 lbs and 15.6 lbs, respectively, the force required to expel Artecoll was estimated to be approximately 13% and 20% of the average maximum lateral finger/thumb forces for men and women, respectively.
- ?? *Syringe leak* – The integrity of the interface seal between the syringe tip and the syringe cap for Artecoll pre-filled syringes was assessed. In tests with 12 devices, each pre-filled syringe was found to hold a pressure of 20 pounds per square inch (PSI) for more than 5 minutes without a decrease in pressure greater than 1 PSI. This reflected a good integrity for the syringe tip/syringe cap seal.

Biological Testing – Biocompatibility testing for Artecoll was performed with the final product.

- ?? *Cytotoxicity* – A sample of Artecoll was tested based on the ISO-10993-5 guidelines. In this test, a positive control (i.e., tin-stabilized polyvinylchloride), a negative control (i.e., high density polyethylene) and 0.1 ml of Artecoll were placed on agarose surfaces that directly overlaid a confluent monolayer of L-929 mouse fibroblasts. After incubation at 37C for 24 hours, no evidence of cell toxicity (i.e., decolorization or lysis of cells) was observed with the control and Artecoll samples. In conclusion, the performance of the positive and negative controls demonstrated that the test was valid. Artecoll was also found to be less cytotoxic than a grade 2 (mild reactivity) material.
- ?? *Genotoxicity* – The mutagenicity of Artecoll was assessed in a reverse mutation assay with strains of histidine-dependent *Salmonella typhimurium* (TA98, TA100, TA1535 and TA1537) and tryptophan-dependent *Escherichia coli* (WP2uvrA) in the presence and absence of S9 metabolic activation. The assay was conducted as described in ISO-10993 guidance. In this test, negative (i.e., saline solution) and positive controls (i.e., p-dimethylaminobenzene diazosulfonic acid sodium salt) were also evaluated. The results demonstrated that the assay was valid and that Artecoll was non-mutagenic to the *Salmonella typhimurium* and *Escherichia coli* strains.
- ?? *Sensitization* – A guinea pig maximization test was performed with Artecoll as described in ISO 10993 Part 10. In this analysis, Artecoll was injected i.d. and occlusively patched onto 10 guinea pigs, while the control (i.e., 0.9% NaCl USP solution) was applied similarly to 5 guinea pigs. After a recovery period, the test and control animals were challenged with patches of Artecoll or control. All sites were then scored at 24, 48 and 72 hours after patch removal. The results of this study demonstrate that Artecoll did not cause a delayed dermal contact sensitization reaction.
- ?? *Implantation in rabbits* – Muscle tissue implantation studies were performed based on the recommendations in ISO 10993, Part 6. In this study, Artecoll and negative controls (polyethylene strips) were each implanted at 4 different sites in three New Zealand White rabbits. After 1 week the animals were euthanized and muscle tissues were examined macroscopically and microscopically. Under the conditions of this study Artecoll was not found to cause a significant macroscopic reaction compared to control. Microscopically Artecoll was judged to be a non-irritant.
- ?? *Implantation in humans and mice* – In this study cross-linked collagen, hyaluronic acid, silicone oil, PMMA microspheres (ranging in size from 4-40 microns), PMMA microspheres in hyaluronic acid (40 microns), polylactic acid microspheres (40 microns), dextran microspheres (40 microns), Trisacryl-gelatin microspheres, silicone particles, pyrrolytic carbon coated with ZrO beads (212 – 500 microns) suspended in 3% beta glucan and polyacrylamide were implanted into humans (s.c. into the volar forearm) or mice

(see below). After injection the clinical appearance of each implant was evaluated every other week and excisions were made after 3, 6 and 9 months. Biopsy samples were HE or Masson Trichrome stained and reviewed by a masked pathologist.

In 44 female mice the same materials were administered either subdermally or intramuscularly into the cheek, axilla, groin, urethra and quadriceps muscle. After 1, 3, 6 and 9 months one mouse in each group was euthanatized and the implantation sites, adjacent lymph nodes and distant organs (liver, spleen, lungs, muscle and urethra) were excised and histologically examined.

The results of the human and mice implantation studies were similar with all implant sites apparent after 1 and 3 months and some undetectable after 6-9 months. In mice, no migration or transportation of any of injected particular filler substance to lymph nodes or filter organs could be detected. In these studies cross-linked collagen and hyaluronic acid were phagocytosized at 6 and 9 months, respectively. Microspheres of polylactic acid caused a mild inflammatory response and disappeared by 4 months. Dextran microspheres caused a pronounced foreign body response and disappeared at 8 months. Silicone particles caused the most pronounced foreign body reaction with a considerable amount of giant cell-persistence. Polyacrylamide injection was well tolerated, but disappeared clinically at 5 months. Trisacryl-gelatin microspheres caused little foreign body reaction, but were absorbed from the skin by 6 months. Polyvinylhydroxide microspheres were well tolerated and stable over 9 months like PMMA microspheres.

?? *Size Dependence of Spherical Tissue Fillers and Phagocytosis* – The phagocytosis of PLA and PMMA microspheres ranging in size from 4.3 to 72 microns were determined by incubation with U-937 macrophage, XS 106 and XS 52 Langerhans cells as well as HaCaT keratinocytes. The extent of phagocytosis was determined by light and confocal microscopy and also fluorescence activated cell sorting. The expression of TNF $\alpha$  after microparticle exposure was also determined.

U-937 macrophages, keratinocytes and Langerhans cells phagocytosized PMMA microspheres smaller than 20 microns. Microspheres greater in size than 20 microns were not ingested by cells. Only collagen coated PLA microspheres stimulated TNF $\alpha$  secretion by U-937 cells.

#### Other Biological Studies on the methylmethacrylate (MMA) monomer of PMMA.

?? Pages 10-011 to 10-022 of Volume 10 summarize the published information on the toxicology and carcinogenicity of PMMA and its monomer (methylmethacrylate). This information includes summaries from “The World Health Organization International Agency for Research on Cancer” (i.e., a review of the chemical carcinogenicity of PMMA and MMA), “The National Toxicology Program” (i.e., investigations on the dose-dependent carcinogenic effects of long-term daily systemic MMA exposure in rodents) and “Published

reports on the safety of implant PMMA”, (i.e., including cytotoxic, inflammatory and immunologic tissue responses to PMMA microspheres particles).

In conclusion, the biocompatibility tests and animal studies presented show an acceptable response to PMMA. Tests on the biological response to microspheres demonstrate that particles greater than 20 microns are not phagocytised. The submitted data also demonstrate that MMA has been removed by PMMA bead processing and the hence the risk of sensitization is low.