Biocompatibility and Surrounding Tissue Response to the Buprenorphine ER Biodegradable Polymer Matrix

The determination of ER biodegradable polymer biocompatibility and other information in this bulletin is based upon reports from veterinarians and the study cited below.

- It is important to recognize that placing a biodegradable material in a biological environment will initiate a response to the bodies perceived infringement and activate mechanisms to effect a healing reaction.
- While inflammation, wound healing and foreign body reaction are considered parts of the tissue responses to “injury”, intensity of the inflammatory response greatly contributes to the biocompatibility and successful administration of a drug delivery system.
- When properly injected into a substantial, unrestricted subcutaneous body region, studies verified that the overall inflammatory response remained low, without scarring, tissue necrosis, or suppuration.
- If however, the ER formulation goes intradermally it can disrupt the dermal microvascular bed and has also been shown to cause severe localized necrosis due to improperly administered intramuscular injections.
- The extent and magnitude of inflammatory reactions when these polymers react with muscle tissue has been documented as a granulation tissue type of healing response with the presence of macrophages, fibroblasts and foreign body giant cells. (See Fig. 1)
- While the muscle tissues surrounding the injection site do not show irreversible changes, the soft tissue reactions to these materials in an intramuscular environment leads to formation of a connective tissue capsular lesion with localized, low-level inflammation mainly of granulation of tissue. (See Fig. 1)
- During the course of degradation, the intramuscular implantation lesions are gradually replaced by collagenous tissue and continue to dissipate with time. (See Fig 1.)

Notes Regarding Risk of Feline Injection-Site Sarcomas

1. ZooPharm has received no reports of FISS from Buprenorphine ER injections following administration to over 100,000 feline patients since 2011.
2. Recent studies (including Srivastav et al. in JAVMA, 2012) suggest that risk factors for FISS in cats are related to long term corticosteriod injections and adjuvanted vaccines.

Fibrous capsule formation surrounding the degrading SR polymer implant following intramuscular tissue involvement

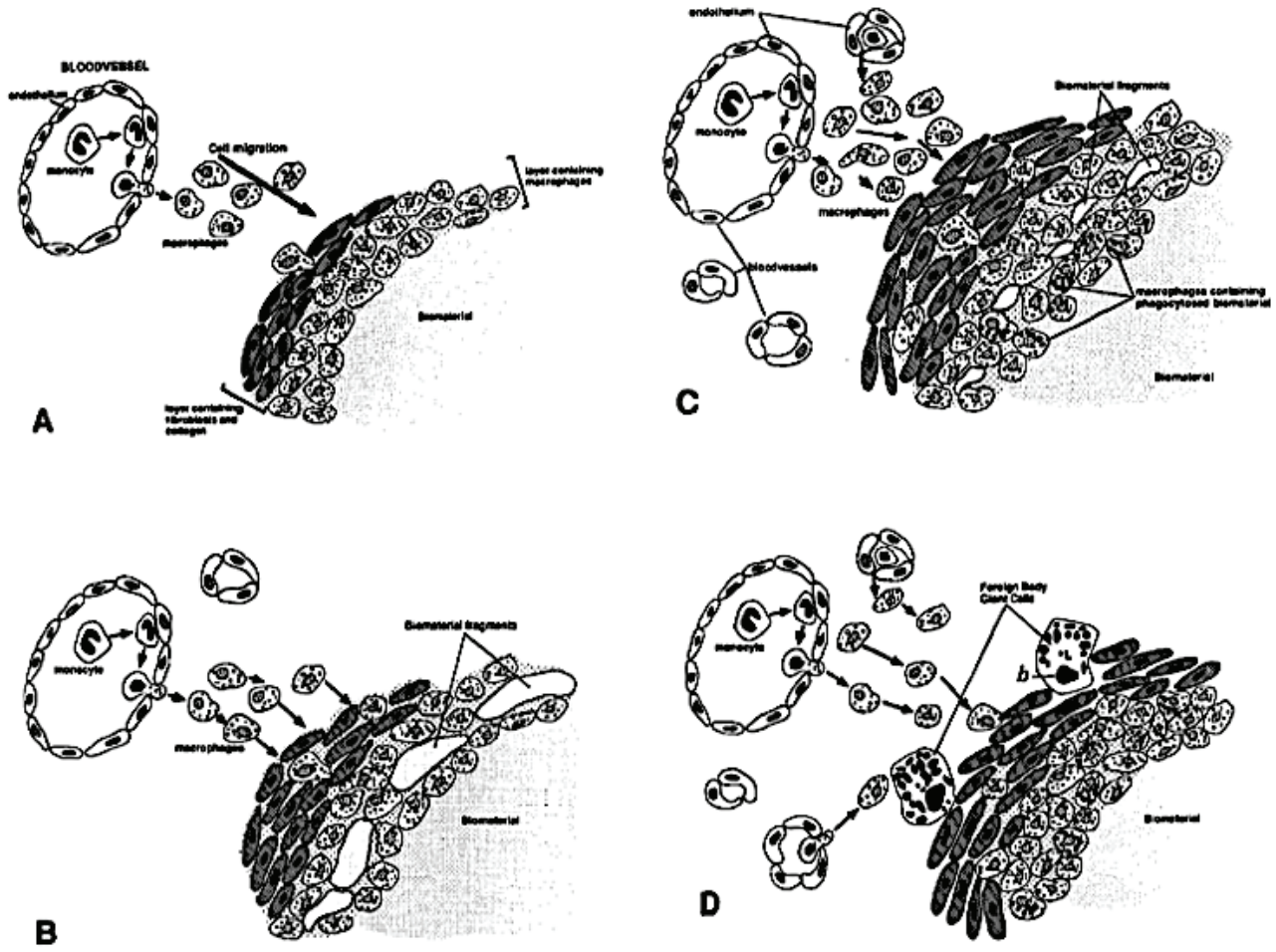

Figure 1. A fibrous capsule forms surrounding a degrading poly(DL-lactide-e-caprolactone) following intramuscular tissue involvement. (A-D) shows the process of capsular formation 2-4 weeks after implantation; migration of macrophages toward the biomaterial to reinforce the fibrous capsule; the outer part of the biomaterial lesion starts to fragment and begin capsular dissipation; bulk of biomaterial continues to decrease with time, as the fragments of biomaterial also became smaller; degradation continues until lesion is fully resorbed without incident.
NOTE: These injection site occurrences can take over 4-5 weeks to completely resolve.

SOURCE: Den Dunnen, W. F. A., Robinson, P. H., Van Wessel, R., Pennings, A. J., Van Leeuwen, M. B. M., & Schakenraad, J. M. (1997). Long-term evaluation of degradation and foreign-body reaction of subcutaneously implanted poly (DL-lactide-ϵ-caprolactone). *Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials and The Japanese Society for Biomaterials*, *36*(3), 337-346.