

# Recommendations for Medical Device Implantation in Swine

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### ABSTRACT

Swine have become a primary preclinical experimental surgical model over the past decade. Their use for the development of medical devices continues to increase as regulatory acceptance of the species for these studies has been achieved internationally. To a large degree the use of domestic and miniature breeds has led to the development of a body of literature justifying their anatomic and physiologic similarity to humans. Likewise the development of technical procedures for anesthesia, surgery and perioperative care have made it easier for laboratories unfamiliar with the species to successfully adapt to their usage. It is likely that swine will continue to be a primary non-rodent preclinical model and that they will increasingly replace dogs and nonhuman primates in studies submitted to regulatory agencies.

**Key Words:** Swine, miniature swine, surgery, medical device.

### INTRODUCTION

Medical devices include those applied externally, implanted devices which have externalized components and devices which are implanted systemically. Such devices may be used in swine clinically, such as analgesic patches. Devices may also aid in the conduction of an experiment, such as catheters or vascular access ports for vascular sampling procedures. Swine are utilized as animal models for the preclinical testing of devices which ultimately are meant to be used for diagnosis, treatment or prevention of disease processes in humans. Such devices include stents, monitoring devices, pacemakers, surgical aids such as new closure devices and any such device that is implanted or deployed intravascularly, into a body cavity or into a tissue or organ (1).

In depth descriptions of surgical procedures in swine have been published (1), including a recent manuscript on the regulatory aspects of preclinical trials in minipigs using medical devices (2). This manuscript will deal mainly with the aspects of using swine as regulatory models in preclinical trials using implanted medical devices.

### REGULATORY REQUIREMENTS

The International Standards Organization (ISO) has developed standards for the preclinical testing of medical devices which have largely been accepted internationally. Their testing standards for implanted devices in animals are detailed in ISO-10993: Biological Evaluation of Medical Devices. Depending upon the specific characteristics of the device it may require adherence to up to 20 of its task requirements within that section (3).

The Food and Drug Administration (FDA) requirements are generally in accord with the ISO-10993 standards (4). However, they may require additional evaluation procedures particularly if the device is made of a new material or leaches therapeutic agents. Most countries have an agency similar to the FDA which may have variations on these requirements. The FDA prefers that preclinical trials of medical devices in animals follow the requirements of the Good Laboratory Practices Act (GLP) which is primarily an auditing and documentation requirement (5). The FDA has made exceptions for adherence to GLP procedures for devices if

the ISO-10993 standards have been followed and the devices are made of previously approved materials deemed to be safe in humans and which are not expected to leach toxic products. They also prefer that implanted test devices be similar in size to the device expected to be implanted clinically in humans.

Israel has a medical device regulatory agency, AMAR, within the Israeli Ministry of Health (6). The agency in general accepts device approvals from the EU and USA or other countries with an acceptable standard of regulatory approval. Written proof must be provided from an agency such as the FDA that their standards were followed and the device has been approved.

Although not required within the various regulatory statutes, accreditation of the animal care and use program by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC) is a validated method of ensuring that the animal care components of the various regulations are in compliance with their standards (7). Our laboratories are accredited and follow all of the guidelines recommended by the NIH Guide for the Care and Use of Laboratory Animals.

The duration of the study is dependent upon its ultimate clinical use in humans. Generally devices can be characterized as having limited (<24 hours), prolonged (1-30 days) or permanent (>30 days) use. When planning the experiment with the goal of achieving FDA or other regulatory agency approval, there should be a meeting with the agency to determine the duration and types of group exposures they will require in order to accept the data. For devices implanted systemically for long term use, the study groups frequently requested are 1 month, 3 months, 6 months and 12 months (2).

As a general rule miniature breeds of swine are used for the chronic exposure groups (1, 8). It is highly recommended that acute experiments be performed in swine, which may be domestic breeds, to obtain pilot data and to determine if procedural or device modifications are required before committing to a GLP study. This is because any data performed as a formal GLP study need to be included in the data submitted to the FDA. Frequently medical devices which work as anticipated in an *in vitro* experiment develop unforeseen problems when implanted in animals (1, 8, 9). Typically domestic breeds are not used for experiments beyond 30 days unless growth is part of the study. The exponential growth of the domestic farm breeds is a complication to these studies

because organs such as the heart or the great vessels will also grow and devices can become detached. Use of the miniature breeds is advantageous if the device is eluting therapeutic agents since their smaller body size compared to domestic breeds requires the use of less test substance. There are approximately 45 breeds of miniature pigs available internationally. The most common commercially available breeds found in the device literature are Hanford, Yucatan, Sinclair and Göttingen. Farm pigs grow from 0.5 to 100 kg in 4 months whereas the various miniature breeds will range from 9-42 kg at sexual maturity at 4-5 months of age (1, 8, 10, 11).

The purpose of these various regulations and standards is to ensure that medical devices have proven biocompatibility, safety and efficacy. They are also meant to be an assurance to the regulatory agencies and the public that the standard of care of the animals and the experimental procedures performed have adhered to a high standard which can be duplicated by other laboratories.

## PORCINE MODELS

### Cardiovascular System

Swine have a number of anatomic and biologic characteristics which make them a suitable model for preclinical testing of medical devices (1, 10, 12, 13). The porcine cardiovascular system is of major importance because of the pig's susceptibility to experimentally induced myocardial infarction and atherosclerosis as well as the similarity to human physiology of wound healing and coagulation within the vasculature. The aorta has a true *vaso vasorum* unlike many other large animal models. If the device needs to approximate the size that will be implanted in humans, sexually mature Hanford pigs have the heart and blood vessel size which most closely approximates that of humans and they will achieve human body weight and organ size within a year. The Yucatan and Göttingen breeds are frequently used as the porcine model for studies which involve the induction of atherosclerosis with or without diabetes and testing of devices or implants related to the treatment of the conditions (1, 10, 12, 13).

Caution should be used when implanting intravascular devices because of the growth of the cardiovascular system. The pig has been used as a growing heart model because of this characteristic. The growth of the heart from birth to sexual maturity at 4.5 months of age in swine is analogous to the growth of the human cardiovascular system from birth to

the mid teenage years. In the domestic pig the aorta will grow 25-30% in length and 35-40% in diameter over a year (1).

### **Integumentary System**

The porcine integumentary system is frequently used for transdermal toxicology and wound healing studies because of the similarities to humans in term of wound healing pathway, dermal metabolism and dermal turnover. Swine integument is useful for studying the effects of topical patch treatments and device implantations which have exteriorization through the skin as part of the study. Swine have been utilized as a primary model for the development of plastic surgical techniques such as grafting and flaps. The skin varies considerably in thickness over various areas of the body. In particular males can develop a very thick epidermis and dermal layer of skin over the dorsum of the neck. The area of skin which is most comparable to humans is located on the lower flank (1, 8, 12).

### **Digestive System**

The digestive system of pigs has been utilized for medical device studies that include interventional laparoscopic studies, natural orifice transluminal endoscopic surgery, development of tumor ablation catheters and anti-obesity device surgery. The similarity to humans of physiology of digestion and the metabolism of nutrients by the intestinal tract, liver and pancreas are primary reasons for the selection of porcine models for these types of studies (1, 8, 12).

Anatomically the pig has a number of unique characteristics of the gastrointestinal tract (1, 8, 12). The stomach has a muscular outpouching in the pyloric region, the torus pyloricus. The small intestine has a unique distribution pattern of the mesenteric vessels; they branch in the subserosa of the intestinal wall rather than forming vascular arcades in the mesentery. The bile duct and pancreatic duct enter the duodenum separately. The majority of the large intestine and the cecum are coiled in a series of centrifugal and centripetal coils located in the left upper quadrant of the abdomen. From there it passes into the descending colon and rectum.

### **Neurologic System**

The brain of the pig has been difficult to access using catheterization techniques due to the presence of the rete mirabile which prevents catheters from passing at the circle of Willis. This structure also prevents the passage of blood clots or microspheres. However, implantation of anti-thrombotic

devices in the vascular system to prevent ischemic stroke has been performed. Implantation of devices into the rostral cranium such as for the collection of cerebrospinal fluid has to take into account that the cranium grows in thickness as the pig ages. Also the sinuses of the pig expand caudally and increase in volume with growth and these two issues may result in failure of a chronically implanted device (1, 8).

### **Urogenital System**

The urogenital system of the pig is closely analogous to that of the human in anatomy and function (1, 8, 12). The kidney and bladder have been used in studies requiring stents and monitoring devices for pressure measurements. The kidney is multirecinate and multipapillate with a true calyceal system analogous to that of the human. The ureter of a 25 kg pig is similar in size to that of humans. The male urethra is not able to be accessed via retrograde catheterization due to the anatomy of the penis. Obstacles are the presence of a prepeutial diverticulum, a corkscrew shaped tip to the penis, and a sigmoid flexure in the penis at the level of the pubis. The bladder wall is thin and friable, characteristics which can make it easily damaged during surgical implantation of bladder catheters. The female may be catheterized in the usual manner.

The male reproductive system has all of the accessory sexual glands which are found in the human but they vary in their relative sizes (1, 8, 12). The prostate gland in swine is small and almost vestigial and the bulbourethral glands are the more dominant structures. The female reproductive system is typical for animals which have litters. The uterus is bicornuate, there is an extensive cervical passage and the fallopian tubes are extremely long and torturous. The fallopian tubes of an 80-100 kg pig approximate the size of that of the adult human. The reproductive system has been utilized for the implantation of sterilization devices.

### **Musculoskeletal system**

The bones and muscular tissue of swine are massive and have rarely been used in medical device studies. The epiphyses of the smaller breeds of miniature pigs may close as early as 1.5 years but in domestic breeds and larger minipigs they may not close until 4.5 years of age with other breeds falling in between those ages. The temperomandibular joint and the articular cartilage of the stifle (knee) joint are two areas with demonstrated similarities to humans. Craniofacial and spinal studies have become an area of interest because of the need

to develop techniques to correct traumatic injuries, which have increasingly occurred as a result of international terrorism. Implants for accelerating closure of bony defects are of particular interest (1, 8, 12).

As a general surgical model, devices have been implanted in many systems and tissues and it is likely that the usage of pigs for these types of studies will increase as more sophisticated models are developed.

### SURGICAL PREPARATION ISSUES

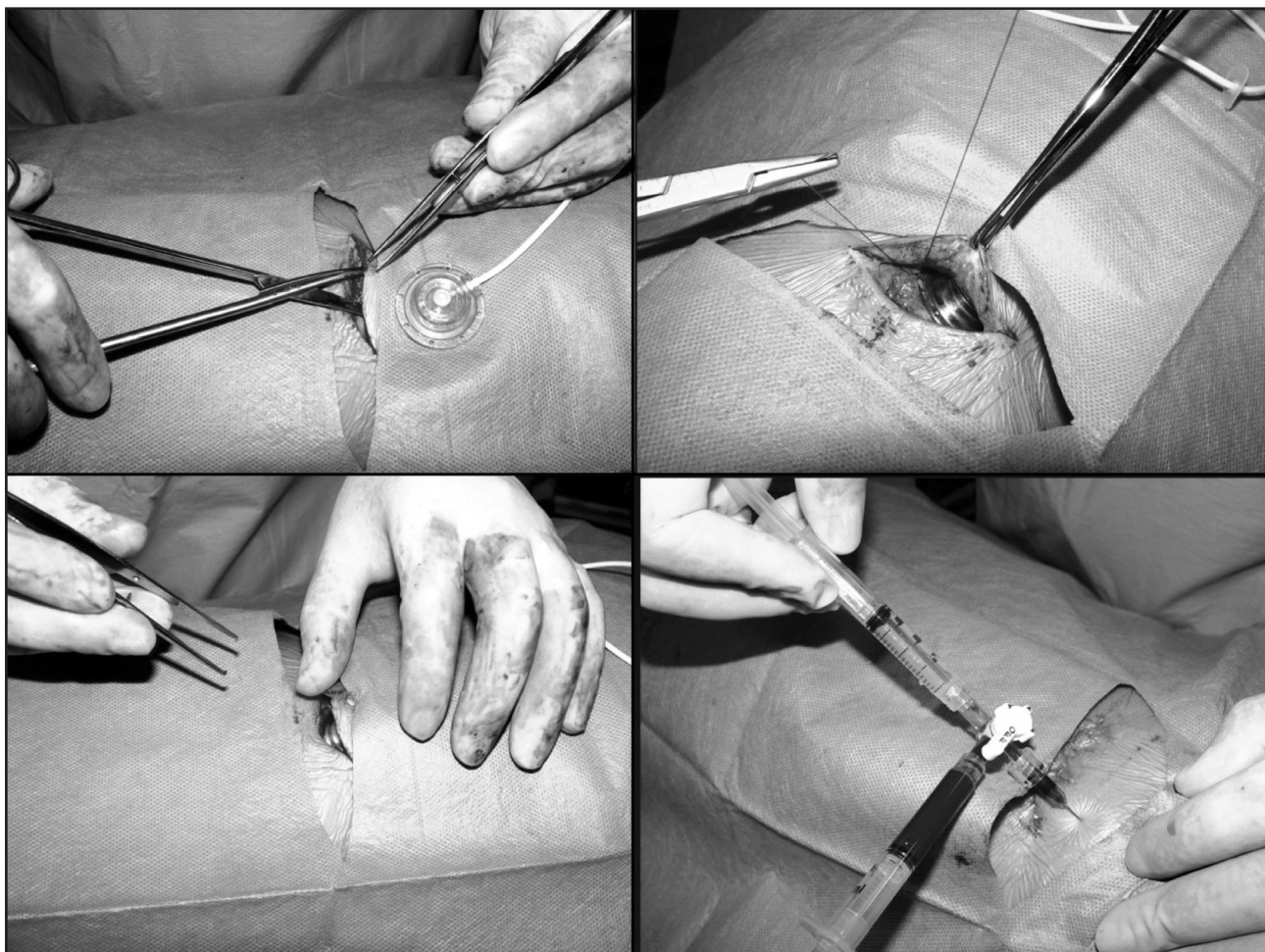
Unless a procedure requires attention to the specific physiology of an organ the anesthetic protocol used is generally not an issue. Exceptions would include protocols involving device implantation in heart failure models or implants into the intestinal tract which change peristalsis or intestinal transport time. For example some anesthetics such as tiletamine-zolazepam have been implicated as a factor in cardiodepression and its use should be avoided in projects involving heart

failure (1, 14). Complete reviews of porcine anesthesia have been published (1, 15, 16). Preemptive analgesia is administered during the preoperative preparation with opioids, Non-Steroidal Anti-Inflammatory Drugs (NSAID) and/or local anesthetics (1, 15-17). Careful selection of anesthetic and analgesic regimens which do not complicate the protocol is an essential element of the planning process. Prophylactic intravenous antibiotics are administered in the preoperative period in order for there to be a protective level at the time of the skin incision. Postoperative antibiotics are only necessary if there is a known contamination or if the surgery is performed in an area with the possibility of having a high level of bacteria such as the colon or oral cavity (1).

A key issue in surgical implantation of devices is sterility of the implant procedure. The principles of surgery specific to the porcine species have been published in detail. In brief, a key issue to remember is that none of the skin preparations sterilize the skin of the animal or the surgeon. A number of



**Figure 1.** The abdominal incision of the pig has been completely prepped for an intraabdominal implant using a circular wound protector applied following application of an iodine impregnated sticky drape.



**Figure 2.** Stepwise implantation of a vascular access port.

skin preparations have been accepted to reduce the bacterial load on the skin and the methods preferred in our laboratories will be described (1).

In the preoperative preparation room the skin is shaved and alternating scrubs of a disinfectant scrub solution are alternated with alcohol rinses. In the operating room a fully gowned surgeon repeats the same sequence of scrubs with a sterile prep kit. After drying the skin with a gauze sponge, an iodine impregnated adhesive surgical drape is applied to the skin. The pig is then completely draped with disposable paper drapes. The incision is made through the adhesive drape and consequently the device to be implanted never contacts the skin. For abdominal procedures a flexible circular wound protector is inserted into the incision (Figure 1). It can also be used for other cavity incisions.

## SURGICAL RECOMMENDATIONS FOR DEVICES

The general principles of surgery are asepsis, closure of dead space, hemostasis, gentle handling of tissues, careful approximation of the wound, avoiding tension and minimizing foreign material. These should be followed meticulously when implanting devices; however, there are some principles of surgery which are specific to implanting devices into swine (1).

Swine have inflammatory reactions to certain suture materials. Silk, surgical gut and antimicrobial coated suture materials have all been demonstrated to have a high incidence of inflammation, sometimes followed by seromas and/or infections. Our preferred methods of closure of muscular and subcutaneous tissues are continuous patterns with absorbable Vicryl or PDS. Porcine skin is particularly amenable to clo-

sure with subcuticular suture patterns which is the recommended method for closure. Vicryl is the preferred suture material however Monocryl may be used if the subcuticular layer is not under undue tension in young animals. The skin incision should not be closed with staples or external skin sutures. Our experience is that staples accumulate feces, food and bedding which can lead to a high incidence of wound infections. Wound infections can be a significant cause of failure of implanted devices. After the subcuticular skin closure is completed a layer of tissue glue is applied to seal the incision thereby providing extra protection in the immediate postoperative period (1).

When implanting subcutaneous devices the pocket should be created distant away from the skin incision so that no portion of the device is beneath the incision (1, 18, 19). Any device implanted subcutaneously should be securely sutured in place to avoid movement. Ethibond is our preferred permanent suture for implantation of devices or catheters in any part of the body. If the post-implantation period is less than two months, PDS may be substituted for Ethibond. Secure closure of the subcutaneous and subcuticular layers will protect against seromas, one of the more common complications to implantations of this type.

Implantation of devices such as pacemakers or telemetry systems is best performed in the intramuscular layers of the neck (1, 18, 20). The incision is made in the jugular furrow between the muscle bodies of the brachiocephalic and sternocephalic muscles. This area is ideal for these types of devices because they tend to have large diameters and heavier weights. They also typically require intravascular insertion of some of their components such as pacemaker leads. The vessels that can be isolated and used from this location are the external jugular vein, internal jugular vein, carotid artery, superficial cervical artery and superficial cervical vein. Our experience is that implantation of these types of devices in the intramuscular plane is more secure and less likely to have complications than subcutaneous implantation.

Implantation of catheters or vascular access ports (Figure 2) can also utilize the cervical incision described above for vascular insertions (1, 18, 19). Intravascular catheters should have suture retention beads securely glued in place prior to insertion of the catheter. The catheter length and location for placement of the beads should be determined in advance. For example, when performing an intravascular catheter implantation in the external jugular vein the tip of the catheter

should be at the entrance of the precava into the right atrium to take advantage of the turbulent flow in that area which will help prevent clotting at the catheter tip. The entry to the atrium is located at the third rib. Two of the three suture beads are inserted into the blood vessel and the third one is positioned at the venotomy site. Placing sutures between the beads prevents migration of the catheter out of the vessel postoperatively.

Catheter design is extremely important in preventing complications. The most common material used for catheters is silicone. This material is porous and can absorb extraneous materials into the catheter walls which can lead to postoperative reactions to the implant. It is best to order catheters from commercial sources with good quality control procedures. Rounded catheter tips are less likely to injure vessel walls and produce blood clots than ones in which the catheter has been cut with a square or angled tip (1, 19).

If a catheter is exteriorized it should have its exit site on the dorsum of the pig (1, 18, 19). Pigs are unable to chew their own surgical sites or to scratch them with their legs in this region. They will rub against the side of their pens or get the site dirty when lying on their sides or ventral abdomen. Consequently, the dorsum is the most protected area to prevent external trauma to exteriorized devices.

Catheters or vascular access ports require flushing and refilling of the catheter with premeasured amounts of an anticoagulant solution once or twice a week. Anticoagulant therapy can be performed with either heparin or taurolidine citrate solution. Catheters should be flushed aseptically with sterile saline and refilled with a premeasured amount of either solution 1-2 times per week. Taurolidine citrate solution offers the advantage of being antimicrobial obviating the use of antibiotics in the catheter which can lead to bacterial resistance (1, 19).

## NECROPSY TECHNIQUE

In general for medical devices the Israel Ministry of Health accepts US Food and Drug Administration (FDA) or Conformité Européenne (CE) approval for use within Israel. However, further validation is needed for certain electro-medical devices which can be obtained from the Israel Standard Institute.

In order to obtain approval for device usage in humans, a complete necropsy needs to be performed on all animals involved in device studies. There are specific guidelines provid-

**Table 1:** Initial evaluation and supplemental evaluation tests for consideration

Body contact		Contact duration A < 24 hr B 24hr – 30d C >30d (permanent)	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Systemic toxicity (acute)	Sub-chronic toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic toxicity (Supplemental test)	Carcinogenicity (Supplemental test)
Surface devices	Skin	A	X	X	X							
		B	X	X	X							
		C	X	X	X							
	Mucosal membrane	A	X	X	X							
		B	X	X	X	O	O		O			
		C	X	X	X	O	X	X	O		O	
	Breached or compromised surfaces	A	X	X	X	O						
		B	X	X	X	O	O		O			
		C	X	X	X	O	X	X	O		O	
External communicating device	Blood path –indirect	A	X	X	X	X				X		
		B	X	X	X	X	O			X		
		C	X	X	X	X	X	X	O	X	X	X
	Tissue/ bone / dentine communicating	A	X	X	X	O						
		B	X	X	O	O	O	X	X			
		C	X	X	O	O	O	X	X		O	X
	Circulating blood	A	X	X	X	X		^		X		
		B	X	X	X	X	O	X	O	X		
		C	X	X	X	X	X	X	O	X	X	X
Implant device	Tissue / bone	A	X	X	X	O						
		B	X	X	O	O	O	X	X			
		C	X	X	O	O	O	X	X		X	X
	blood	A	X	X	X	X			X	X		
		B	X	X	X	X	O	X	X	X		
		C	X	X	X	X	X	X	X	X	X	X

X – ISO evaluation test for consideration.

O – additional test which may be applicable.

^ – for all devices used in extracorporeal circuits.

Adapted from 510(k) Memorandum-#695-1 Table 1 Initial Evaluation Tests for Consideration and Attachment B-Table 2 Supplementary Evaluation Tests for Consideration, from the FDA websites:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/guidancedocuments/ucm080742.htm>

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/guidancedocuments/ucm080752.htm>

ed by regulatory agencies as to which tissues to collect based on the type of device. If the device has reached the stage of being implanted, many tests have already been performed on the device including biocompatibility of components used in the device. After the device has been implanted for the predetermined length of time, a complete necropsy needs to be performed on all animals included in the study, including unexpected or unexplained mortalities and morbidities (21).

Collection of tissues and histological analysis is dependent both on the regulatory agency evaluating the submission as well as the type of device. Tissues sampled are determined based on length of time the device is implanted for as well as where in the body the device is implanted. For example, a device that is in contact with skin for less than 24 hours will have different necropsy requirements than a permanent device in contact with circulating blood (Table 1).

**Table 2:** Consider inclusion of the following assessments in your evaluation of cardiovascular devices

• Endothelialization
• Mural injury
• Inflammation
• Vascularization
• Intimal fibrin
• Intimal and medial smooth muscle cell proliferation
• Adventitial fibrosis
• The integrity of the internal and external elastic laminae

Adapted from the FDA website: <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm220760.htm>

The necropsy is typically used to assess local tissue changes from mechanical disruption or changes in blood flow. The minimal tissues to be collected include those immediately surrounding the device. If the device is placed internally, then refer to Table 1 as a reference for evaluation considerations.

Information that needs to be in the report to the evaluating agency includes gross necropsy information with detailed description of the device site and photographs of lesions and device site. Evidence of responses to the device including inflammation (acute or chronic), and other physiologic changes should also be noted (22). Swine are a premiere species used in cardiovascular device testing due to many factors. If a cardiovascular device is being evaluated, the degree of vessel disruption, cellularity, mineralization, and disruption of lamina are all required to be evaluated (Table 2). Also important is to determine if the device is affected by the animal – is the device still structurally sound and functional to do what it is designed to do. The US FDA also recommends scanning electron microscopic studies of the site to characterize surface behavior of the endothelium adjacent to the implant, explant radiography, and histology of local and downstream tissues.

## DISCUSSION

The anatomic and physiologic comparisons to humans discussed above are a primary reason for the development of swine as preclinical models for the implantation of medical devices (1,12). Equally important has been the development of anesthesia and surgical procedures which improve success rates (1, 15, 16). Using the technical procedures described above our laboratory has a vast amount of experiences since

1985 with medical device implants with a minimal complication rate. Sterility of the implantation procedure and proper selection of suture materials is an absolute factor for long term success. Using the anesthetic, analgesic and perioperative care techniques recommended ensures that projects will be conducted in a non-stressful and humane manner for the pigs (1, 23, 24). Unless growth is part of the study then miniature breeds should be used for the chronic projects. Continued growth of the domestic breeds over several months will cause failure of devices implanted in many organs and structures. For example the major blood vessels increase in both length and diameter as body size continues to increase (1, 8). Projects and perioperative care methods should be designed both to ensure that the project is conducted humanely and that it achieves scientific success (17, 23, 24). The recommendations made by our laboratory for these procedures have proven to be valid for conducting research involving medical devices.

## CONFLICT OF INTEREST

The authors declare that they do not have any conflict of interest associated with this manuscript.

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