University of Massachusetts Medical School
Registration Number 14-R-0035
Addendum to Annual Report of Research Facility (Form 7023)
Fiscal year 2019

Explanation of Category E Studies:
Category E *in vivo* testing was performed under Dockets A-2184 and A-2207, of the Massachusetts Biologic Laboratories (MBL), located at the University of Massachusetts Medical School University Campus using death as an endpoint assays mandated by the Code of Federal Regulations. The assays are mandatory and required in order for MBL to maintain licensure to manufacture and distribute vaccine products.

A-2184 (60 Guinea pigs)

21 CFR 610.1 and 21 CFR 610.10 (requirement for potency testing of each lot of FDA licensed biological product)

21 CFR 211.166 (requirement for a stability testing program for FDA licensed drug products)

Diphtheria potency testing uses death as an endpoint. The current assay does not allow for the use of analgesics without FDA approval. Any pain-relieving drugs used to alleviate pain or distress may alter the disease progression in the established model and may interfere with interpretation of the results.

A-2207 (84 Guinea pigs)

21 CFR 211.84 (Requires the testing of each lot of drug components to be used in manufacture. The Public Health Service, National Institutes of Health, dated March 1, 1947 (tetanus) and revision December 15, 1952 (diphtheria) stipulate that the potency of the parent toxin must be evaluated either by in vivo titration against standard antitoxin or by the MLD method. Both methods involve toxin induced symptoms and death of guinea pigs as an end-point. The MLD method can be accomplished using fewer animals and thus is selected for use.

Tetanus and diphtheria MLD assay: death by intoxication is the required assay endpoint. The current assay does not allow for the use of analgesics without FDA approval. Any pain-relieving drugs used to alleviate pain or distress may alter the disease progression in the established model and may interfere with interpretation of the results.

A-2532-18: Cat. E: Swine (1)

Justification: This project is a final preclinical development of AAV gene therapy for atrial fibrillation. As listed on the protocol, pain-relieving drugs are used for post-operative pain control, especially for first 72 hours after the procedure and any breakthrough pain will be treated with additional narcotic and NSAID. Other than drugs that affect the atrial fibrillation substrate or ventricular repolarization, treatment of pain or distress is not limited. Mechanisms of atrial fibrillation differ depending on the presences or absence of heart failure. This study is designed to evaluate responses of subjects with atrial fibrillation and heart failure to gene therapy. The sustained elevation in ventricular rate from the pacing causes a tachycardiomyopathy. This is intentional because heart failure alters atrial fibrillation, and is essential to the model. In this protocol, we use atrioventricular nodal ablation and ventricular pacemaker implantation to take control over the ventricular rate response and thereby better control the level of left ventricular dysfunction. Even with this step, the severity of heart failure will vary to some extent from one animal to the next. The human situation is similar with considerable variability in symptoms at the same left ventricular ejection fraction. Any drugs or interventions that have any potential to affect vulnerability to atrial fibrillation or eliminate heart failure cannot be used. Therefore, Animals in Category E, may develop severe signs that can't be relieved by appropriate drug use." In addition to the issue of signs in spite of appropriate drug use, drugs that may affect the development of or sustaining atrial fibrillation (i.e. drugs that affect cardiac electrophysiology, cardiac inflammatory or fibrotic response, or drugs that alter cardiac metabolism or apoptosis) cannot be used because they interfere with the disease process under study. Drugs that are routinely used to treat human heart failure (vasodilators, diuretics) must be used with extreme caution in pigs because the drug response is often exaggerated, and the animals conditioned deteriorates rather than improves.