MICHELSON PRIZE DATA PACKAGE-2 (DP-2) REQUIREMENTS

Introduction

The package is comprised of three main sections:

A. Development of Final Formulation or Manufacturing Specifications
B. Pivotal Safety Study
C. Non-Pivotal Effectiveness Study

Since the specific requirements for this data package are product candidate-specific, the Foundation will develop the study plans, in consultation with the applicant, before work is started. All three sections must be completed under Good Laboratory Practices (GLP) or Good Clinical Practices (GCP) using a contract research organization (CRO) approved by the Foundation that has expertise in clinical and manufacturing programs consistent with FDA CVM regulatory requirements and guidelines. An INAD (Investigational New Animal Drug; section 512(j) of the FFDCA) file must be opened with the Center for Veterinary Medicine (CVM) before initiation of any pivotal studies associated with these program elements. (The INAD application includes sponsor definition, e.g. the entity that is responsible for all regulatory submissions.) Groups unfamiliar with FDA CVM procedures should seek Foundation help and guidance as needed.

Section A. Development of Final Formulation or Manufacturing Specifications

Final formulation with manufacturing specifications must be completed satisfactorily prior to beginning the safety and effectiveness studies that follow. This section includes the methods, facilities, and controls required for manufacturing, processing, and packaging of the product candidate sufficient to preserve its identity, strength, quality, and purity.

The following three key deliverables must be met or exceeded:

1. Production of a minimum of three consecutive product batches at individual batch sizes that are no less than $1/10^{th}$ of the final batch size that will be produced during commercial manufacturing. For example, if the anticipated final batch size is 50,000 doses, then at least 5,000 doses/batch that are produced in 3 consecutive batch runs, should be produced. Each batch must satisfactorily pass test requirements for identity, strength (potency), quality, and purity as approved by the Foundation.

2. Demonstration of formulated product stability for a minimum of 6 months (real-time). Stability studies must be conducted in the immediate container under the storage conditions (temperature, humidity, etc.) that will be used for the commercial product. Each batch must satisfactorily pass test requirements for stability to predict reasonable stability under the anticipated storage conditions of the final commercial product as approved by the Foundation.
3. Completion of preliminary packaging studies. Preliminary packaging studies must be conducted in the immediate container and outer packaging that will be used for the commercial product and approved by the Foundation.

Section B. Pivotal Safety Study

The purpose of this study is to demonstrate that the product candidate is safe in the target animal species when used according to the proposed product label (route of administration, dose, age, etc.). The information collected in the study will be used to fulfill, in part, the Target Animal Safety technical section of the NADA (New Animal Drug Application). The CRO study must be conducted in healthy animals of each species and gender for which the product is intended (dog and cat, males and females). The two major goals of the study are:

- to identify any harmful (adverse) drug effects, and
- to establish a margin of product candidate safety through evaluation at multiple escalating doses above the proposed (1X) dose.

For each study, the product candidate produced under section A (Final Formulation Development) must be administered in a single dose using the route and delivery method intended for final use. All study results must be documented for Foundation review.

1. ***Study Design***. The standard (label) 1X dose must be based on, and justified by, the target host species margin of safety and toxicology results obtained in Data Package-1. The study protocol requires FDA CVM concurrence (i.e. must be submitted for FDA CVM review and approval) before study initiation, and the study must be performed at a CRO acceptable to the Foundation. A minimum of 128 total animals in a study design of minimum 12 months' duration is required, including (minimums):

- Four treatment groups tested: appropriate placebo, 1X dose, and at least two higher doses (e.g. 3X, 5X)
- Two species tested: canine and feline
- Two genders tested: males and females
- Two age groups tested: pre- and post-pubertal
- Four animals per group
- *[4 treatments x 2 species x 2 genders x 2 age groups x 4 animals/group = 128 animals]*

2. ***Study Readouts***. Product candidate safety information must be collected using all the following methods:
   - Observations. Must include a minimum of physical exams, body weight and body appearance, general behavior, food consumption, and fecal exams.
   - Serum chemistry concentrations. Must include a minimum of the standard parameters in **Appendix 1** for each species.
   - Hematology. Must include a minimum of the standard parameters in **Appendix 1** for each species.
   - Urinalysis. Must include a minimum of the standard parameters in **Appendix 1** for each species.
   - Gross pathology and histopathology findings. All animals must have a full gross pathology necropsy, with organs and tissues (**Appendix 2**) collected from all groups. In addition, the tissues from placebo and highest dose animals must have full histopathology examinations. Should there be histopathology findings in animals from the highest dose group, histopathology on other groups may be required. Gross pathology and histopathology examinations must be conducted by a board-certified veterinary pathologist.
   - Other. Depending on mechanism of action, other readouts may be required, such as electrocardiogram data, bone density measurement, etc.

3. ***Study Results***. Copies of all raw data must be included. Appropriate statistical methods must be used to assess comparisons between placebo and treated animals in all measured parameters. Analyzed data for individual readouts must be presented in tables, figures, images or other summary formats. A separate legend and description for each analyzed data set must be included.

4. ***Study Discussion and Conclusions***. Interpretation of study results for each data set must be provided, and main conclusions summarized.

Section C. Non-Pivotal Effectiveness Study

The purpose of this study is to demonstrate effectiveness and field safety in a small population of the target animals to serve as a basis for the pivotal effectiveness studies required by the FDA CVM. The information collected in the study may be used as part of the Effectiveness technical section of the NADA.

Ideally, the study is initiated after completion of the Pivotal Safety Study, but these are sometimes conducted concurrently. The major goals of this study are:

- to demonstrate that the product candidate will provide continuous, ongoing sterility for a minimum of 3 consecutive years in male and female dogs and male and female cats, and
- to demonstrate probability of permanence, e.g., show with predictable probability that the product candidate will work as a permanent sterilant in the target animal species when used according to the product label, and
- to collect field safety data in each target animal species and sex at the dose intended for the product label.

The study can be conducted through a CRO or in the field using client-owned dogs and cats. The product candidate produced under section A (Final Formulation Development) must be administered in a single dose using the route and delivery method intended for the product label. The study should be conducted under GLP/GCP guidelines, and all results must be documented and included for Foundation review. Definition of permanent suppression of

fertility and ablation of sex steroids and/or their effects must be provided and justified prior to study initiation.

1. ***Study Design***. The study protocol requires Foundation approval before study initiation.
   - Treatment groups must be composed of a minimum of 10 males and 10 females for each species (dog and cat) in both pre- and post-pubertal animals. (Note: this number must be based on appropriate power calculations and may need to be higher, depending on the power calculation from preliminary data.)
   - Each treatment group must receive 1X dose.
   - Depending on mechanism of action, each treatment group must be followed for a minimum of 3 consecutive years. Study duration may be:
     - shorter if conclusive evidence of permanent sterility is demonstrated, or
     - longer if interim time points show evidence of or probability of reversibility.

2. ***Study Readouts***. Evaluation of sterility and probability of permanence at multiple, periodic time points during the minimum 3 year study is required. Product candidate effectiveness information must be collected using scientifically validated, scientifically accepted, and/or scientifically justified (based on mechanism of action) methods. Scientific method examples include (but are not limited to): serum testosterone, estradiol and/or progesterone concentrations, histology of testicular and ovarian tissues, etc. The study may be discontinued by the Foundation if fertility returns during the monitoring window.

3. ***Study Results***. Copies of all raw data must be provided. Appropriate statistical methods must be used to assess comparisons between placebo and treated animals in all measured parameters. Analyzed data for individual readouts at

each data collection time point must be presented in tables, figures, images, or other summary formats. A separate legend and description for each analyzed data set must be included.

4. ***Study Discussion and Conclusions***. Interpretation of study results for each data set must be provided and main conclusions should be summarized.

APPENDICES

Appendix 1. Serum chemistry, hematology urinalysis panels, minimum parameters.

Appendix 2. Major tissues and organs to be collected for gross pathology and histopathology in Study Readouts, minimum parameters.

Appendix 1. SERUM CHEMISTRY, HEMATOLOGY URINALYSIS PANELS, MINIMUM PARAMETERS.

Required Serum Chemistry Panel

- alkaline phosphatase
- total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dL)
- aspartate aminotransferase
- alanine aminotransferase
- gamma glutamyl transferase
- sorbitol dehydrogenase
- urea nitrogen
- creatinine
- total protein
- albumin
- globulin and A/G (albumin/globulin) ratio (calculated)
- glucose
- total cholesterol
- triglycerides
- electrolytes (sodium, potassium, chloride)
- calcium
- phosphorus
- urea

Required Hematology Panel

- leukocyte count (total, relative and absolute differential)
- erythrocyte count
- hemoglobin
- hematocrit
- mean corpuscular hemoglobin
- mean corpuscular volume
- mean corpuscular hemoglobin concentration (calculated)
- absolute reticulocytes
- platelet count
- blood cell morphology
- prothrombin time
- activated partial thromboplastin time

Required Urinalysis Panel

- volume
- specific gravity
- pH
- color and appearance
- protein
- glucose
- bilirubin
- ketones
- blood
- urobilinogen
- microscopy of centrifuged sediment

Appendix 2. MAJOR TISSUES AND ORGANS TO BE COLLECTED FOR GROSS PATHOLOGY AND HISTOPATHOLOGY IN STUDY READOUTS, MINIMUM PARAMETERS.

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination
Adrenal gland	X	X	X
Aorta		X	X
Bone with bone marrow, femur		X	X
Bone with bone marrow, sternum		X	X
Bone marrow smear[a]		X	
Brain (cerebrum, midbrain, cerebellum, medulla/pons)	X	X	X
Epididymis	X	X	X
Esophagus		X	X
Eye (with optic nerve)		X	X
Heart	X	X	X
Kidney	X	X	X
Large intestine, cecum		X	X
Large intestine, colon		X	X
Large intestine, rectum		X	X
Liver	X	X	X
Lung with bronchi		X	X
Lymph node, mandibular		X	X
Lymph node, mesenteric		X	X
Mammary gland (process females only)		X	X
Nerve, sciatic		X	X
Ovary (record morphology, presence of follicles and corpora lutea)	X	X	X
Oviducts		X	X
Pancreas		X	X
Peyer's patch		X	X
Pituitary	X	X	X
Prostate		X	X
Salivary gland, mandibular[b]	X	X	X
Salivary gland, parotid		X	X
Salivary gland, sublingual		X	X
Seminal vesicles with coagulating gland	X	X	X
Skeletal muscle, biceps femoris		X	X
Skin		X	X
Small intestine, duodenum		X	X
Small intestine, ileum		X	X
Small intestine, jejunum		X	X
Spinal cord, cervical		X	X
Spinal cord, lumbar		X	X
Spinal cord, thoracic		X	X
Spleen	X	X	X
Stomach, glandular		X	X

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination
Stomach, nonglandular		X	X
Target Organs[c]		X	X
Testis	X	X	X
Thymus	X	X	X
Thyroid gland (with parathyroid)[d]	X	X	X
Trachea		X	X
Urinary bladder		X	X
Uterus with cervix	X	X	X
Vagina		X	X
Gross lesions		X	X
Tissue masses with regional lymph node[e]		X	X

[a] Bone marrow smears will be prepared only for animals necropsied at scheduled intervals. Evaluation will be performed at the discretion of the Study Director and/or Sponsor.

[b] The combined weight of the right mandibular/sublingual salivary gland will be obtained.

[c] Target organs (and target organ gross lesions) will be designated by the Study Director, Pathologist and/or Sponsor based on experimental findings.

[d] Parathyroids cannot always be identified macroscopically. They will be examined if in the plane of section and in all cases where they are noted as grossly enlarged.

[e] A regional lymph node drains the region where a tissue mass is located. A regional lymph node may not always be identified when a mass is present.