MICHELSON PRIZE DATA PACKAGE-1 (DP-1) REQUIREMENTS

Applicants should refer to the **Michelson Prize and Grants Research Quality Assurance Toolkit** at www.michelsonprizeandgrants.org/resources/qa-toolkit for quality assurance practices and data that are required for Data Package-1. Toolkit references below refer to quality practices described on that website.

Section A. Preliminary Data

Preliminary data are defined as the entirety of results obtained in all studies completed from project inception up to the point immediately prior to the initiation of studies associated with the specific safety and effectiveness data sets required in sections B and C, respectively. The goal of this section is to provide a clear summary of the project history and scientific progress that led to the applicant's decision to advance the program to complete the safety and effectiveness sections outlined below (sections B and C).

All *in vitro* and *in vivo* studies for which data sets exist must be presented and summarized in this section. Data presented cannot be pre-selected for, or only restricted to, positive safety and effectiveness results. It is important to include all negative results that may have failed to meet the safety and effectiveness target thresholds set for preliminary studies. Similarly, unexpected results, outcomes, and data that may be inconsistent with the original scientific theory and associated mechanism of action(s) hypothesis must also be presented.

Toolkit Section 5

This section must include a short summary for each of the following subsections:

1. Brief Description of Project History
    a. ***Research Team, Institution(s), and Funding Source(s)***. Provide a list of the research team members, showing the Principal Investigator, all Co-Investigators, and affiliated institutions(s) for each individual. The funding source(s) that supported all the preliminary work should be listed, including amount, duration, Principal Investigator, and funded study title(s).
    b. ***Scientific Theory***. Provide a clear, succinct statement of the hypothesis supported through repeated testing results (e.g., accumulated evidence from preliminary data provided herein, or in published studies from other laboratories that support the principal hypothesis).

Toolkit Section 1

c. ***Scientific Approach***. Provide a brief summary of scientific approach(es) used to test the hypothesis. Include description of the most important methods used to obtain all the relevant outcomes that were measured (e.g., clearly explain how safety and effectiveness were assessed).

Toolkit Section 3

d. ***Animal Models Used***. Provide a summary of all laboratory animals (e.g., rodents, rabbits), cat, dog, and any other animal species used to generate the preliminary data.

2. Summary of Scientific Data – Provide all preliminary data for all *in vivo* (animal studies), *ex vivo,* and/or *in vitro* studies using samples from animal studies. For each study conducted, the following should be provided:

- ***Study Title***.
- ***Study Purpose***. State primary and secondary (if any) objectives.
- ***Species and Sex***. List all laboratory animals, cat, dog, and any other animal species in which the candidate was tested. Indicate the gender (female and male) and reproductive status (pre-pubertal, post-pubertal).
- ***Numbers Used***. List number of laboratory animals used.
- ***Study Duration***. List the total length of the in-life laboratory animal phase, including any interim time points at which laboratory animals were euthanized.
- ***Results (Outcomes) Measured***. Succinctly describe the techniques and methods used to measure each outcome measured.

Toolkit Sections 3, 4

- ***Results***. Provide in the form of a table, figure, image, diagram, etc. Include separate legend and description for each data set presented in order for each result to stand on its own (without supporting discussion text).

Toolkit Section 5

- ***Result Interpretation***. Provide a brief, interpretative summary for each result presented.

3. Summary of Scientific Results

Toolkit Section 5

- ***Positive Outcomes*** (successes). Briefly list all the results that support the scientific theory and/or satisfy (meet or exceed) the decision criteria for project progression to enter the Data Package-1 preliminary safety and effectiveness phase (e.g., data presented in

sections B and C, below). Include all results that are consistent with results obtained from published studies from other laboratories using similar scientific approach(es) and readouts.

- ***Negative Outcomes*** (failures). List all the results that failed to support the scientific theory and/or did not meet study goals for safety and/or efficacy.
- ***Unexpected Outcomes***. List all the results that were not predicted and/or influenced how the preliminary safety and effectiveness studies (presented below) were subsequently conducted. Include any results that differed from results obtained from published studies from other laboratories using a similar scientific approach(es) and readouts.

Section B. Safety

The purpose of this section is to provide a summary of all rodent and target species (cats and dogs) studies conducted under the minimum experimental designs outlined below. Data sets are intended for use in defining the target dose for the DP-2 Pivotal Safety Study.

1. Dose Definition

Toolkit Section 3

   a. ***Target (1X) dose***. Provide the proposed dose (1X) for each species (rodent, cat, dog) and for each sex (and for reproductive status i.e. pre- or post-puberal?).
   b. ***Justification***. Provide a brief rationale and any relevant result summary information (e.g., preliminary data, section A) that support the 1X target dose selected for each species.

2. Toxicology Studies

Toolkit Sections 3-5

   Depending on the product candidate's chemical or molecular structure, genotoxicity studies are required that should be consistent with the International Conference on Harmonization (ICH) Draft Guidance document [S2(R1) Genotoxocity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use; 2008 – **Appendix 1**]. A standard test battery is suitable and must include a test for gene mutation in bacteria, and genotoxicity evaluation in mammalian cells *in vitro* (e.g., mouse lymphoma L5178Y *tk* gene mutation assay) and/or *in vivo* (micronuclei assay using

rodent hematopoietic cells). Depending on the experimental design, integration of the *in vivo* genotoxicity assays into the dose escalation rodent safety study may be acceptable to the Foundation.

3. Rodent Safety Studies

These studies must be conducted and completed prior to initiation of the target animal safety studies. The purpose of these studies is to provide data generated under the minimum experimental design that is likely to be predictive of acceptable safety in the target animal species (Section B.4). In all studies, the product candidate must be administered one time by the identical route and method intended for the target animal safety studies.

Toolkit Sections 3-5

a. ***Study Design (minimum)***. In order to evaluate both the long term safety and margin of safety of a treatment anticipated to have a permanent effect, the in-life phase must be at least 12 months in duration. At a minimum, the following 4 treatment groups must be included: placebo, 1X (target) dose, a medium dose, and a high dose. The medium and high doses are defined by the applicant; however, the medium and high doses should be at least two and five times the 1X dose, respectively. Post-administration time points for data collection must include: acute (2-4 weeks), intermediate (3 months), and final (12 months). Depending on the mechanism of action of the treatment, the Rodent Safety study may be designed as a combined safety and effectiveness study (see Rodent Effectiveness study, C1, below).

Toolkit Section 5

b. ***Study Readouts***. At a minimum, the following five principal measurements of candidate safety must be conducted:

Toolkit Sections 3, 5

   i. Daily observations. Must include general behavior and appearance.
   ii. Weekly observations. Must include body weight, and brief physical examination.
   iii. Gross pathology. Must include all major tissues/organs/body systems and reproductive tissues specified in **Appendix 2** at a minimum of the 3 required time points (acute, intermediate and final) in the study design.
   iv. Histopathology. For all groups and time points, must include reproductive tissues, and, for high dose group, must include all major tissues/organs/body systems specified in **Appendix 2.** For medium

and low dose groups, if histopathology in high dose group identifies any pathology in a specific tissue/organ/body system, then that specific major tissue/organ/body system must also be analyzed at a minimum of the 3 required time points in the study design to define margin of safety.

v. Serum chemistry and hematology. Standard panels with minimum tests specified in **Appendix 3** must be run at a minimum prior to dosing and at the intermediate and final time points required in the study design.

c. ***Study Results***. Copies of all raw data must be submitted. Appropriate statistical methods should be used to assess comparisons between placebo and treated animals in all measured parameters. Analyzed data for each of the five principal measurements of candidate safety should be presented in tables, figures, diagrams, images, or other summary formats. A separate legend and description for each analyzed data set should be included.

Toolkit Sections 3-5

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

e. ***Safety Risk/Mitigation Strategy***. Safety knowledge gaps for which key information may be missing due to the experimental design selected and/or results obtained should be identified, together with any recommendations on how these gaps might be addressed through experimental design modifications in target animal safety studies.

4. <u>Target Animal (Cat and Dog) Safety Studies</u>

Toolkit Sections 3-5

Target species safety studies must be conducted and completed as part of the Data Package-1 requirements. The purpose of these studies is to produce acute safety data using a study design that will determine the doses in the cats and dogs of each sex to be used in the Data Package-2 (DP-2) Pivotal Safety Study, to follow. Studies must be performed in pre- and post-puberal male and female dogs and cats, and the product candidate must be administered one time by the identical route, and method, intended for the DP-2 Pivotal Safety Study, to follow. Furthermore, the treatment should be

composed/formulated/manufactured in a way to assure similarity and consistency to the final form to be used after full development. All results (positive, negative, and unexpected) must be documented and presented.

a. ***Study Design***. In-life phase must be at least 1 month in duration. Treated animals of each species and sex should receive a single administration of the product candidate in the form and by the route expected to be used in the later DP-2 pivotal safety study. The dose is defined by the applicant, but, at a minimum, must be at least twice the target (1X) dose. The principal aim is to identify any treatment adverse effects (AEs), generally defined as any unexpected side effects or unintended changes in the structure, function, or chemistry of the body, including injury, toxicity, and sensitivity reactions.

Toolkit Section 3

b. ***Study Readouts***. At a minimum, the following four categories of observations of candidate safety must be included:

Toolkit Sections 3-5

   i. Daily observations. Must include general behavior, body appearance, and food consumption.
   ii. Weekly observations. Must include physical examination, body weight, standard serum chemistry and hematology profiles (**Appendix 3**), and standard urinalysis (**Appendix 4**).
   iii. Other. Depending on mechanism of action, other readouts may be required, such as electrocardiogram data, bone density measurement, etc.
   iv. Gross pathology and histopathology (**Appendix 2**). Euthanasia is not required in this study, but, if any animals die, a full necropsy is required, with complete histopathology performed to determine, if possible, the cause of death.

c. ***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 all daily and weekly observation readouts of candidate acute safety should be presented in tables, figures, images, or other summary formats. A separate legend and description for each analyzed data set should be included.

Toolkit Section 5

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

e. ***Safety Risk/Mitigation Strategy***. Safety knowledge gaps for which key information may be missing due to the experimental design selected and/or results obtained should be identified, together with any recommendation on how these gaps might be addressed through experimental design modifications in the DP-2 Pivotal Safety Study.

Section C. Effectiveness

Toolkit Sections 3-5

These studies must be conducted and completed for Data Package-1. The goal of this section is to provide a comprehensive summary of rodent and target species (cats and dogs) studies used to define the target effectiveness dose for later use in the DP-2 non-pivotal target host effectiveness study that will follow Foundation acceptance of DP-1. For each effectiveness study outline below, clearly stated definitions must be provided for:

- "Suppression of fertility and ablation of sex steroids and/or their effects" using at least one scientifically accepted or scientifically valid measurement.
- "Probability of permanence" using at least one scientifically accepted or scientifically valid measurement OR valid justification based on the product candidate mechanism(s) of action.

In all studies, the product candidate must be composed/formulated/manufactured in a way to assure similarity and consistency to the final composition intended for DP-2 non-pivotal target host efficacy study and during full development. The product candidate must be a single administration by the identical route and delivery method intended for the DP-2 non-pivotal target host efficacy study and during full development. Post-puberal animals should be used unless the applicant can justify that the effect will be different in pre-pubertal animals. All results (positive, negative, and unexpected) must be documented and presented.

1. <u>Rodent Studies</u>
   - Must demonstrate complete suppression of fertility and ablation of sex steroids and/or their effects in both females and males for a minimum of 12 consecutive months.

- Must demonstrate probability of permanence through data trend line that shows no expectation of recovery or rebound.
- May need to demonstrate longer than 12 consecutive months depending on mechanism of action or if data trend line shows possible recovery or rebound.
- Depending on the mechanism of action of the treatment, the Rodent Effectiveness Safety study may be designed as a combined safety and effectiveness study (see Rodent Safety study, B3, above).

2. Female Dog Studies
   - Because the inter-estrous interval in female dogs is variable and can be up to 24 months, this study must demonstrate complete suppression of fertility (no estrous cycle) and ablation of sex steroids and/or their effects for a minimum of 24 consecutive months.
   - Must demonstrate probability of permanence through data trend line that shows no expectation of recovery or rebound.
   - May need to demonstrate effect for longer than 24 consecutive months depending on mechanism of action or if data trend line shows possible recovery or rebound.
3. Male Dog Studies
   - Must demonstrate complete suppression of fertility and ablation of sex steroids and/or their effects for a minimum of 12 consecutive months.
   - Must demonstrate probability of permanence through data trend line that shows no expectation of recovery or rebound.
   - May need to demonstrate effect for longer than 12 consecutive months depending on mechanism of action or if data trend line shows possible recovery or rebound.
4. Male and Female Cat Studies
   - Must demonstrate suppression of male and female fertility and ablation of sex steroids and/or their effects for a minimum of 12 consecutive months in cats housed under constant or long (>14 hours) day-length photoperiod.
   - Must demonstrate probability of permanence through data trend line that shows no expectation of recovery or rebound.

- May need to demonstrate effect for longer than 12 consecutive months depending on mechanism of action or if data trend line shows possible recovery or rebound.

Section D. Mechanism of Action

Toolkit Sections 3, 5

The primary objective of this section is to define the mechanism(s) by which the pharmacologically active substance (e.g., drug or vaccine) or device generates the antifertility (e.g., sterilant) effect in rodents, cats and dogs. Provide answers or address each of the following:

1. How does the product candidate work? Identify and describe the specific target and/or biochemical pathway by which the candidate exerts its mode of action (MOA) (sterilant effect). If the product candidate has more than one MOA, each target should be discussed separately, followed by a brief summary of any known additive or synergistic anti-fertility effects.
2. If applicable, define the structure-activity relationship (SAR). Describe the relationship of the chemical or molecular structure of the product candidate with respect to its biological activity. If the structure has been quantitatively correlated with the biological activity (QSAR), provide the mathematical relationship (formula) used to predict the biological response of related chemical structures.
3. Why does the product candidate result in permanent suppression of fertility and ablation of sex steroids and/or their effects? List the measurable scientific parameters on which the conclusion is based for each species. Examples include (but are not limited to): serum testosterone, serum estradiol, serum progesterone, and testicular and ovarian histology.
4. Based on the MOA, provide any safety related issues or concerns that will be important to monitor in the DP-2 pivotal safety study, including need for personal protective equipment for persons handling the product candidate.

Section E. Pre-Final Formulation Composition

Toolkit Sections 3, 5

If the treatment is a drug, this information is required. This section provides a foundation for the Chemistry, Manufacturing, and Controls (CMC) technical section of the FDA Center for Veterinary Medicine New Animal Drug Application (NADA). The objective

of this section is to provide assurance that the product can be made at commercial scale in a manner that would be acceptable for approval by the FDA.

Provide a comprehensive list and description of all the individual components in the product candidate. List each ingredient that will be used to make the product.

1. Outline how the product candidate might be made at commercial scale. Demonstrate that there is reasonable probability that the compound can be made at commercial scale by, for example, describing the key steps in the outline of production and manufacture scale at which the product is most likely to be produced.
2. Provide a concept of labeling. Describe the proposed immediate container and outer packaging. Describe the type of vial, bottle, syringe, and/or packet that the product itself will be in contact with.
3. Storage conditions and shelf life. Provide a summary of any real-time or accelerated stability studies conducted to evaluate degradation, by-products, solubility, moisture content, etc.

Section F. Statistical Justification of Sample Size and Statistical Analysis

Toolkit Sections 3, 5

The objective of this section is to provide a statistical justification of the number of animals used in each treatment group and in each study completed to assess product candidate safety and effectiveness. Describe the statistical methods and power analysis used to determine treatment sizes to analyze the safety and effectiveness results for each of the safety and effectiveness studies listed above.

Section G. Quality Assurance

The purpose of this section is to provide a summary of the quality, scientific practices used to assure the reliability, reproducibility, and relevance of the entirety of scientific data provided in Data Package-1.

The Michelson Prize & Grants program administrators recognize that all grant applicants, grantees, and prize registrants are committed to performing sound scientific research with traceable and repeatable processes that assure data integrity and confidence in research findings. It is understood that studies in Data Package-1 may not be conducted under GLP (Good Laboratory Practices) and GCP (Good Clinical Practices), as these studies

are not intended to be pivotal for regulatory approval. Therefore, in order to support the recommended voluntary quality practices of researchers funded by FAF, the Foundation has provided a **Quality Assurance Toolkit** to help researchers meet quality assurance objectives as a means to promote the credibility and acceptability of their work. The FAF Quality Assurance Toolkit was designed to provide opportunities for incorporating quality assurance features into typical research environments and was based on selected recommendations provided by the World Health Organization (WHO Handbook: Quality practices in basic biomedical research, ISBN; 92 4 159445 4, 2006) and the British Association for Research Quality Assurance (BARQA, Guidelines for Quality in Non-Regulated Scientific Research, ISBN: 1-904610-08-0, 2006).

Use of the FAF Quality Assurance Toolkit will provide assurance that the quality critical research practices associated with personnel and equipment management and the recommended control of procedures, data, records, and methodology have been implemented throughout the research investigation. References to toolkit sections that will support DP-1 requirements are provided within this document.

It is recommended that all studies conducted adhere to general quality assurance expectations and guidelines as demonstrated by a commitment to an established quality standard, the implementation of a laboratory quality assurance management system, or the use of the FAF Quality Assurance Toolkit in order to sharpen the focus on the sound science and quality practices present in the research program. A site visit to evaluate laboratory capacity to have generated DP-1 data and use, if any, of Toolkit items, will be scheduled upon submission of DP-1 in order to review quality management practices.

Section H. Supporting Information

The objective of this section is to include all information about the product candidate that was not provided in the other sections. Examples of information for this section include:

1. Project publications. Provide copies of all peer-reviewed publications, publications in press, accepted for publication, or submitted manuscripts associated with any of the data provided in Data Package-1.
2. Project summary reports. Provide copies of all draft manuscripts and all reports generated to meet any funding requirements.

3. Relevant references. Provide list of key references that support the scientific theory, approach, animal models, and results associated with any of the data provided in Data Package-1.

APPENDICES

Appendix 1. International Conference on Harmonization (ICH) Guidance Document [S2(R1) Genotoxocity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use; 2012.]

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

Appendix 3. Serum chemistry and hematology panels, minimum parameters.

Appendix 4. Urinalysis, minimum parameters.

Appendix 1. **INTERNATIONAL CONFERENCE ON HARMONIZATION (ICH) GUIDANCE DOCUMENT [S2(R1) GENOTOXOCITY TESTING AND DATA INTERPRETATION FOR PHARMACEUTICALS INTENDED FOR HUMAN USE; 2012].**

Appendix 2. MAJOR TISSUES AND ORGANS TO BE COLLECTED FOR GROSS 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.

Appendix 3. SERUM CHEMISTRY AND HEMATOLOGY 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

Appendix 4. URINALYSIS, MINIMUM PARAMETERS.

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