



The Role of the **Study Director in Nonclinical Studies**

Pharmaceuticals, Chemicals,
Medical Devices, and Pesticides

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FIGURE 12.6. OECD Model 2 Fit to Proportion *Not* Male.

FIGURE 13.1. Schematic Representation of the Coagulation Pathway. Roman numerals represent clotting factors (proenzymes) that require activation to become functional. Roman numerals with "a" represent activated clotting factors. Thrombin is feedback activator of factors XI, VIII, and V. TF, tissue factor; T, thrombin (also *k/a* factor IIa).

FIGURE 16.1. Testes, Rat, H&E. The Left Testis Is Normal. The right testis is smaller and poorly developed, which would be recorded as *hypoplasia, unilateral*. Studies using peripubertal primates and dogs frequently have *bilateral* testes that are not fully mature and are thus small. A *unilateral* finding would be recorded in the histopathology incidence table, whereas the *bilateral* observation may or may not be recorded in the incidence tables as immature when considered a normal given the age of the animal. See color insert.

FIGURE 16.2. Key Personnel on a Toxicology Study Team. A diagram representing the different knowledge areas that must work in synergy to produce an optimal toxicological pathology report.

FIGURE 16.3. Thresholding in Microscopic Evaluation. A pictorial representation of the variability in tissue morphology that one might observe in a typical toxicology study with different doses. A determination of whether or not the variation in tissue morphology is test

article-related or not would require one to know what doses (or exposure) were used in each group. See color insert.

FIGURE 16.4. Bone Marrow, Rat, H&E. These images demonstrate changes in the cellularity of the rat bone marrow at different doses when dosed for 14 days. Compared with the control tissues (0 mg/kg/day), all other groups show reduced or hypocellular bone marrow elements. Additionally, the stroma of the bone marrow changes in the 150 mg/kg/day image from adipose tissue to fibrous connective tissue. *The 150 mg/kg/day dose group was sacrificed after 8 days of dosing due to clinical signs of toxicity. See color insert.

FIGURE 16.5. Submandibular Lymph Nodes, Rat, H&E. These images are taken at the same magnification of lymphoid tissue collected from rats in a 3-month oral gavage toxicity study. Sporadic variation in this tissue was observed in all dose groups. There were no other test article-related findings in the immune system. Therefore, this finding was considered spontaneous normal variation and a background finding. See color insert.

FIGURE 16.6. Kidney, Rat, H&E. These images are taken from rats in a chronic gavage toxicity study in the kidney near the corticomedullary junction. The control kidney is generally unremarkable. The high-dose kidney has findings of degeneration (dilated tubules filled with proteinaceous fluid) and inflammation (mononuclear cell infiltration) that could be lumped under the finding “chronic progressive nephropathy.” See color insert.

FIGURE 16.7. Liver, Rat, H&E. These images are from the liver of two dosed rats in two toxicity studies of varying lengths. The liver in the shorter study has a small number of mononuclear inflammatory cells

accumulating within the parenchyma. The liver in the longer study has a large number of mononuclear inflammatory cells coalescing and additionally forming small granulomas. If these findings were observed at different dosing intervals with the same test article, then alignment of terminology is warranted to indicate that the finding on the left is a more incipient version of the one on the right. See color insert.

FIGURE 16.8. Lung Diagrams. These diagrams provide an example of the importance of macroscopic data to the microscopic examination. In these drawings, necropsy findings are represented by dark areas that have various distributions. The horizontal bar represents the location of the protocol tissue that would be routinely examined in the microscopic examination. The lungs with diffuse and multifocal findings would have these findings end up on the protocol tissue; the lung with the regional finding would require the macroscopic data to ensure that the necropsy finding was examined microscopically.

FIGURE 16.9. Rat Tissue Blocking. Each image in this collection represents a single tissue cassette with a collection of similar fixed and trimmed tissues covering all protocol tissues from a single animal in a toxicity study. The histotechnologist and the pathologist both need to verify that all tissues are accounted for and subsequently examined during the microscopic portion of the study. Note that the bone sections will require decalcification post fixation. Mand., mandibular; LN, lymph node. See color insert.

FIGURE 16.10. Kidney, Rat, Periodic Acid-Schiff (PAS) stain. These images were taken from a toxicity study in which the kidney was identified as a target organ after examination of the H&E slides. The PAS special stain was subsequently added to the examination to better

characterize changes in the tubular epithelium basement membrane. The arrows in the high-dose image points to thickened basement membranes. See color insert.

FIGURE 16.11. Spleen, Rat, Immunohistochemistry. These images demonstrate common chromagen-based immunohistochemistry. The immunoreactive target stains brown after which the nonreactive tissue is counterstained with hematoxylin. The spleen on the left is stained with an anti-CD79a antibody to demonstrate the B cell-rich follicles, while the spleen on the right is stained with an anti-CD68 antibody, which shows a macrophage-rich red pulp. See color insert.

FIGURE 16.12. Liver, Rat, H&E. The liver image from the high-dose group individual has a number of morphological changes to the tissue that warrant description in the microscopic data. One prominent finding in the high-dose liver are the clear spaces of vacuoles in the cytoplasm of the hepatocytes. The preferred descriptive (objective) term for this is hepatocellular vacuolation. A morphological diagnosis that connotes the pathological process might be lipidosis, an etiological diagnosis that connotes the cause might be toxic hepatopathy, and a disease diagnosis used to describe a clinical condition might be drug-induced liver injury. Only the descriptive term of hepatocellular vacuolation should be used for the microscopic data in a toxicology study. See color insert.

FIGURE 16.13. Determining the Reversibility of a Test Article-Related Finding. The primary evidence of reversibility for a test article-related finding is a reduction in the severity/incidence of the finding after an appropriate wash-out period. The diagram indicates

additional consideration that a Study Pathologist may use in making a final determination of reversibility.

FIGURE 16.14. Heart (Coronary Artery), Dog, H&E. The artery from the dog administered the high dose has several morphological changes including disruption to the vessel wall along with the presence of red blood cells (also known as fibrinoid degeneration) and increased basophilic granular material surrounding the vessel. This finding would clearly be considered adverse due to the potential for serious or life-threatening dysfunction of this vital structure. See color insert.

FIGURE 17.1. The Relationship between Administered Dose and Response via the “Black Box” of Toxicokinetics and the Characterization of Absorption, Distribution, Metabolism, and Elimination (ADME) of a Xenobiotic.

FIGURE 17.2. Characteristic Concentration-Time (Toxicokinetic) Profiles for a Drug Administered by Four Different Routes: Intravenous (i.v.), Intraperitoneal (i.p.), Intramuscular (i.m.), and Oral (p.o.).

FIGURE 17.3. Linear Concentration versus Time Profile for A-440 at 100, 200, and 400 mg/kg. Source: Newton (1996).

FIGURE 17.4. Log-Linear Concentration versus Time Profile for A-440 at 100, 200, and 400 mg/kg.

FIGURE 17.5. Log-Linear Concentration-Time Profile of a Xenobiotic in a One-Compartment Model with First-Order Elimination Following i.v. Administration.

FIGURE 17.6. Log-Linear Plasma Concentration-Time Plot of Drug Administered by the i.v. Route where Elimination is of the First Order. The plot demonstrates the distribution phase (α) followed by the elimination phase (β) in a two-compartment model.