Pathology Reporting of Preclinical Studies

Data Integration, Regulatory Expectations and Issues with Pathology Reports; Examples of Pathology Reports

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and

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EPL, Inc.

The Purpose of the Toxicology Evaluation

- Guide clinical development by identifying inherent toxicities of a biopharmaceutical and possibly identifying markers that may be monitored in a clinical study

- Identify hazards due to the test article and how they influence the risk assessment

- To fulfill these requirements, pathology reports must meet the needs of the customer (regulators), while withstanding the scrutiny of colleagues (peer review)

Goals of the Pathology Evaluation

- Identify potential compound-related effects
  - This is a descriptive and interpretive science
- Name alterations, tabulate, and categorize
  - Allows correlations between test article exposure and biological effects
- Fulfill regulatory expectations for the evaluation of safety
  - Reports should be written for the regulatory reviewer's utility

Use of the Pathology Evaluation

- Are identified lesions due to test article?
- Does the identified hazard represent a risk?
- Are the findings critical for understanding safety and relevant to the design of the clinical study or affect the risk assessment?
- Add perspective to the study findings

Responsibility of the Pathologist

- Provide a reliable and detailed description of gross and microscopic changes
  - Consistent evaluation
  - Clear interpretation
  - Concise narrative

- Large volume of data to generate and interpret
  - 40 to 50 tissues/animal

Responsibility of the Pathologist

- Target organ toxicity is important, but each organ cannot be treated as a separate entity

- Separate normal biological variation and spontaneous changes from compound-induced changes
  - Influence of compound on spontaneous changes

- What were the diagnostic criteria for the findings
  - Present where appropriate
  - References are preferable (e.g., INHAND)

Responsibility of the Pathologist

- Nomenclature used by a pathologist should be consistent within a study
  - Diagnostic drift

- Variation of grading among pathologists will not generally affect the overall interpretation of a study
  - One pathologist should evaluate all tissues from a study

Responsibility of the Pathologist

- Attribute relationship to compound
  - Direct versus exacerbation of spontaneous changes
- Perspective on similar lesions induced by other compounds or natural occurrence
- Propose pathogenesis for toxic changes
  - Pattern of tissue changes can provide clues

Pathologist's Report

- Written pathology interpretation
  - Detailed description of findings
  - Clear interpretation and best judgment of importance of findings
  - Concise and explicit wording
    - Avoid pathology jargon
    - Write with simple, concise sentence structure
  - Analysis is based on the treatment cohort rather than effects on individual animals
    - Need to consider individual effects in non-rodent species
    - Adverse = deleterious to the animal whether unintended or related to pharmacology
    - Toxicity does not equal adverse

Pathologist's Report

In-depth discussion with perspective to support safety assessment

- Statistical versus biological importance

Perspective on similar lesions induced by other compounds, a common mechanism of action, or spontaneous changes

Suggestions for Pathology Reports

- Effects should be described qualitatively rather than quantitatively to aid understanding of importance of the findings
  - Grading scales
- If there are no compound-related alterations, simply state that no effects were observed
  - Injection sites in parenteral studies
- Write from the perspective of the regulator
  - The report should be informative
  - Use in-text tables as appropriate
- Begin results by stating what was important
  - "Test article-related lesions were present in organ 1, 2, 3, etc."

What Are Regulators Looking For

- A comprehensive table of test article-related lesions with summary text
  - Correlations to organ weights, clinical pathology, and clinical signs, if possible
- Explanation of diagnostic criteria and grading
  - Description or references
- Criteria used to determine if finding is adverse or not
  - Keller DA, Juberg DR, Catlin N, Farland WH, Hess FG, Wolf DC, Doerrer NG. 2012. Identification and characterization of adverse effects in 21st century toxicology. Toxicol Sci. 126(2):291-297.

Adversity

- Adverse Effect: A change in morphology, physiology, growth, development, reproduction, or life span of a cell or organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.

Keller, et al, 2012

Correlation of Animal Toxicity to Man

- Up to 71% correlation when similar organ systems are affected in both rodent and non-rodent species
- 63% correlation when only non-rodent affected
- 43% correlation when only rodent affected

Olson H, et al. 2000. Reg Toxicol Pharmacol. 32:56-67.

Correlation of Animal Toxicity to Man

- Greatest correlation in predicting human adverse effects in
  - Haematological system
  - Gastrointestinal system
  - Cardiovascular system

- Least predictive for effects on skin and hepatobiliary system

Olson H, et al. 2000. Reg Toxicol Pharmacol. 32:56-67.

Understand the Lesions

- Need a clear, concise explanation of relevance

- Need to know if the lesion is
  - Real or theoretical
  - A risk to humans
  - A class effect

Understand the Lesions

- Is it bad or not?
  - Bad for the animal versus bad for a human
    - Regulators may blur this distinction
- If it is perceived to be bad, need to explain to a regulator why it's an acceptable risk
- Very important to frame the issue appropriately

EXAMPLE PATHOLOGY REPORTS

Title Page

DRAFT REPORT

STUDY PHASE: Pathology

TESTING FACILITY STUDY NO. 2012ABC
EPL STUDY NO. 999-001

A 3-Month Study of ABC-123 by Oral Gavage Administration in Sprague-Dawley Rats with a 28-Day Recovery Period

SPONSOR:
XYZ, Inc.
1003 Main Street
New York, NY 10009

TESTING FACILITY:
DEF CONTRACT LABORATORIES
1123 Jones Lane
Spring, TX 89511

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December 28, 2010

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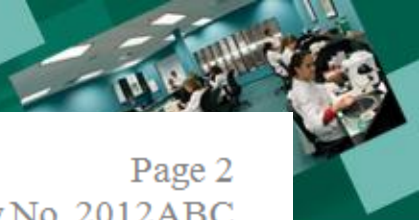
Responsible Personnel



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LIST OF DATA TABLES

1. RESPONSIBLE PERSONNEL

Study Pathologist: Peter C. Mann, DVM, Diplomate, ACVP
Senior Veterinary Pathologist
Experimental Pathology Laboratories, Inc.

Summary

- High Level – limited detail
- Short Description of methods
- Treatment-related effects only

2. SUMMARY

Eighty male and female Sprague-Dawley rats were dosed with test article (ABC-123) or control article [Capmul® Medium Chain Monoglyceride (MCM); Tween 80 (MCM-Tween 80, 95:5 w/w)], via oral gavage daily for 91 days. Six main study animals died before the terminal necropsy; none of the early deaths was due to treatment. In the heart, focal degeneration/necrosis of myocytes with mononuclear inflammation was present in both control and treated male rats. Although there was a slight numerical increase in the Group 4 males, the finding was considered a random spontaneous event, since the incidence was similar to that reported in an earlier study of ABC-123 at the same laboratory, the incidence in the published literature is as high as 100%, and the most severe lesion in this study was less severe than those in control males in the previous study. There were no changes related to the administration of ABC-123 to Sprague-Dawley Rats for three months at doses of up to 2 mg/kg/day.

Introduction/Objectives

- Study Information
- Objective – from Protocol (remember to change to past tense)
- Where parts of study conducted (if applicable

3. INTRODUCTION

This report presents the pathology findings in Sprague-Dawley rats assigned to the study entitled, "A 3-Month Study of ABC-123 by Oral Gavage Administration in Sprague-Dawley Rats with a 28-Day Recovery Period" (Study No. YOW00018). The objectives of this study were to determine the potential toxicity of ABC-123 when given orally by gavage for three months to Sprague-Dawley rats, to evaluate the potential reversibility of any findings, and to provide data to support the use of ABC-123 in humans. In addition, the toxicokinetic characteristics of ABC-123 were determined. The study was sponsored by XYZ, Inc., 1003 Main Street, New York, NY 10009 Gross pathology was conducted at DEF CONTRACT LABORATORIES, 1123 Jones Lane, Spring, TX 89511. Microscopic slide, organ weight, and clinical pathology data evaluation was conducted by Peter C. Mann, DVM, DACVP, at Experimental Pathology Laboratories, Inc (EPL®), Seattle, Washington. Although the in-life portion of this study included a recovery Group (Day 120), the pathology report only covers the terminal necropsy (Day 92).

Materials and Methods

- Words (from protocol)
- Table of Experimental Design
- Necropsy Details
- Fixation details

4. MATERIALS AND METHODS

Eighty male and female Sprague-Dawley rats were dosed with test article (ABC-123) or control article [Capmul® Medium Chain Monoglyceride (MCM); Tween 80 (MCM-Tween 80, 95:5 w/w)], via oral gavage daily for 91 days. The dose administered to rats in each group is shown in the following table.

Group Assignments and Dose Levels					No. Necropsied:	
Group No.	**Number of Males/Females**	**Dose Level (mg/kg/day)**	**Dose Volume (mL/kg)**	**Dose Concentration (mg/mL)**	**Terminal (Day 92)**	**Recovery (Day 120)**
1	15/15	0 (control)	1	0	10/10	5/5
2	15/15	0.5	1	0.5	10/10	5/5
3	15/15	1	1	1	10/10	5/5
4	15/15	2	1	2	10/10	5/5

At termination, a complete gross necropsy was conducted. Protocol-specified necropsy procedures included evaluation of the carcass and musculoskeletal system; all external surfaces and orifices; cranial cavity and external surfaces of the brain; and thoracic, abdominal, and pelvic cavities with their associated organs and tissues, measurement of selected organ weights, and the examination/collection of organs/tissues (see organ weight and tissue/organ collected tables below). Gross observations and organ weights were entered into a validated pathology computer program (Provantis™NT2000, Version 2.1.6 Data Management System). With the exception of the eye and optic nerve (preserved in Davidson's fixative), all tissues/organs were collected in 10% neutral buffered formalin (10% NBF).

Listing of Tissues

- Organs Weighed
- Tissues collected
- Tissues Examined
- Clinical Pathology samples collected (if appropriate)

Tissues Examined and Collected at Necropsy

The following tissues and organs (or portions of), when present, were collected from any animal that was euthanized. Tissues were preserved in 10% neutral-buffered formalin (except for the eyes, which were preserved in Davidson's fixative for optimum fixation).

Tissues Collected	
Cardiovascular	Urogenital
Aorta	Kidneys
Heart	Ureters
Digestive	Urinary Bladder
Salivary Gland (mandibular)	Testes
Tongue	Epididymides
Esophagus	Prostate
Stomach	Seminal Vesicles
Small Intestine	Ovaries
Duodenum	Oviduct
Jejunum	Uterus (with cervix)
Ileum	Vagina
Large Intestine	Endocrine
Cecum	Adrenals
Colon	Pituitary
Rectum	Thyroid/Parathyroids
Pancreas	Harderian Gland
Liver	Skin/Musculoskeletal

Results

- Early Deaths/Mortality
  - Discuss all early deaths
  - Cause of death, if determined
  - Are lesions treatment-related?

5.1. Early Deaths

Six main study rats died before the terminal necropsy on Day 92 and gross pathology findings for early death animals are listed in Appendix 28 of the main study report. One female in Group 2 died on Day 65 and a female in Group 3 died on Day 8. No tissues were submitted for these animals, so it is not possible to determine cause of death (although the Group 2 rat did have an 8.9 cm section of gavage tube present in the esophagus at the time of necropsy). In the Group 4 males, there was an unscheduled necropsy on Day 72 (Animal 4003) and a second animal found dead on Day 24 (Animal 4012). Animal 4003 had malignant lymphoma in multiple organs. Although this rat was somewhat young for lymphoma, the neoplasm is not considered test article-related. The cause of death for Animal 4012 could not be determined. This animal was part of the recovery group. In the Group 4 females, two rats were found dead on Day 30 (Animal 4504) and Day 57 (Animal 4506). Grossly, Animal 4504 had dark gelatinous red material (consistent with clotted blood) in the thoracic cavity, red discoloration of all lung lobes, and a laceration of the right middle lobe of the lung. Microscopically, there was mild edema of the lungs. It is likely that this animal died as a result of a gavage error. The cause of death for Animal 4506 could not be determined.

Gross Pathology

- Treatment-related gross findings
- Correlation with organ weights/histopathology if possible
- If none of the gross findings were considered treatment-related, state: “None of the gross findings were the result of treatment with ABC”

5.2. Gross Pathology

Gross pathology observations for animals euthanized on Day 92 (Terminal Necropsy) are listed in Appendix 20 and Appendix 26 of the main study report. None of the gross observations noted at necropsy were considered to be related to treatment with ABC-123.

Organ Weights

- Treatment-related organ weights
- Absolute and relative weights
- Correlation with gross findings/histopathology if possible
- If none of the gross findings were considered treatment-related, state: "None of the organ weight findings were the result of treatment with ABC"
-

Organ weights – compared to controls

Text Table 2 **Percent Differences in XXX Weights in ABC-Treated Rats Compared to the Vehicle Control (Group 1) Rats – Main Study**

Sex		Males				
Group		**1**	**2**	**3**	**4**	
Dose (mg/kg/day)		**0**	**10**	**20**	**40**	
Number of animals examined		10	10	10	10	10
Prostate						
	Absolute	12	9	9	12	9
	% body	14	15	7	12	20
		Females				
Uterus						
	Absolute	12	25	29	24	40
	% body	11	23	21	25	43

Clinical Pathology

- Hematology
- Coagulation
- Clinical Chemistry
- Urinalysis

Histopathology

- Interim Sacrifice(s)
- Terminal Sacrifice
- Recovery Sacrifice

Order of results

- Neoplastic Findings
- Non-neoplastic Findings

Histopathology – what to report

- Treatment-related findings
- Unusual findings that might need an explanation
- Do not list non-treatment related findings
- Text tables are very useful for specific treatment-related findings

Histopathology

5.5. Histopathology

All microscopic alterations observed were presented in the Table of Individual Microscopic Findings (AOFT) Table II. Histomorphologic findings were graded from one to five (1-5), depending upon severity, present (P) when grading was not appropriate, or as not remarkable (-). All lesions were summarized by treatment group in the Summary Tables Table IC . Gross lesions, along with any corresponding microscopic finding(s), were reported in the Correlation Table: Necropsy-Microscopy Table III.

5.5.1. Neoplastic Findings

One Group 4 unscheduled death male (Animal 4003) had malignant lymphoma present in multiple organs. One terminal-necropsy female in Group 4 (Animal 4507) had a unilateral tubulostromal carcinoma of the ovary, which had invaded the adjacent oviduct. Although the rats in this study are somewhat young to develop neoplasms, both of the tumors occur

Histopathology – Non-neoplastic Findings

3.3.1. Main Study

Test article-related macroscopic findings were seen in the liver, testis, epididymis, spleen and miscellaneous lymph nodes.

In the liver, changes observed in Group 2 and Group 6 rats, included irregular surface, firm, area/foci pale, pale discoloration, area raised and enlargement. Irregular surface and firm correlated with fibrosis and pale area /foci and pale discoloration were associated with liver necrosis (hepatocellular and/or single cell) or vacuolation (hepatocellular) and, in some cases, with mortality in male rats as described above. Enlargement correlated with cyto/karyomegaly in one rat (Animal No. 6011).

In the testis, two Group 2 rats had one or more of the observations of area pale and small Which correlated with testicular necrosis, degeneration/atrophy of the seminiferous epithelium and/or mineralization. One of them (Animal No. 2002) presented small epididymis which correlated with slight oligo/aspermia. The observation of a single, unilateral area pale in a single control male rat had no microscopic correlation and was considered a spontaneous change.

In the spleen, enlargement was seen in five Group 2 male rats (Animal Nos. 2002, 2003, 2006,

Text Tables

Text Table 1: Incidence of Selected Heart Changes in Male Rats

	Group 1	Group 4
(Number examined)	10	11
Degeneration/necrosis with mononuclear inflammation, focal		
-minimal	2	3
-mild	-	1

Final Statment

All of the remaining microscopic changes present at the end of terminal necropsy were of the type and character expected in young laboratory rats and were present at a similar incidence in both the control and high-dose group.

Discussions/Conclusions

- Detailed discussion of treatment-related changes
- Discussion of why pathologist felt certain changes were or were not treatment-related
- List specific references as appropriate
- State NOAEL if appropriate

4 CONCLUSION

4.1. Main Study

Test article-related organ weight changes were present in the liver and spleen following the termination of dosing. In the liver, the mean absolute and relative (to body weight) weights were statistically increased in Group 2 male rats . In the spleen, the mean absolute and relative (to body weight) weights were statistically increased in Group 2 male/female rats and in Group 6 male/female rats.

Test article-related macroscopic changes were seen in liver, testis, epididymis, spleen and miscellaneous lymph nodes. In the liver, changes including irregular surface, firm, area/foci pale and pale discoloration and area raised that were associated with liver necrosis (hepatocellular and/or single cell) or vacuolation (hepatocellular) and enlargement correlating with cyto/karyomegaly. In the testis, two Group 2 rats had one or more of the observations of area pale and small which were associated with testicular necrosis, degeneration/atrophy of the seminiferous epithelium and/or mineralization. One of them (Animal No. 2002) presented a small bilateral epididymis which correlated with slight oligo/aspermia. The observation of a single, unilateral area pale associated with a single control male rat had no microscopic correlated and was considered a spontaneous change. In the spleen, enlargement was seen in male rats treated with SNALP-1955 that correlated usually with histiocytosis and extramedullary hematopoiesis. A few miscellaneous lymph nodes (pancreatic/mediastinal) showed enlargement in rats treated with SNALP-1955 as well as with ALN-VSP02 (5 mg/kg/day) which correlated with lymphoid/stromal cell hyperplasia, histiocytosis and/or suppurative inflammation.

6. CONCLUSIONS

The change diagnosed as focal degeneration/necrosis of myocytes with mononuclear inflammation is a common spontaneous change in young rats, seen predominantly in males (Ruben et al, 2000[1]; Jokinen et al, 2005[2]). Historically, this change has often been diagnosed as "cardiomyopathy" in rodents. It has been suggested (Keenan et al 2010[3]) that the use of "cardiomyopathy" is inappropriate, especially since the changes in the rodent heart bear little resemblance to the human clinical condition of the same name (Roberts and Schwartz, 2000[4]). In an earlier study of ABC-123 conducted DEF Contract Laboratories, 1123 Jones Lane, Spring, TX 89511 (Study No. 20121ABB:: A 28-Day Oral Gavage Repeat-Dose Toxicity Study in Sprague-Dawley Rats with a 28-Day Recovery Period), the same changes were diagnosed as cardiomyopathy. In the earlier study, three of the control male rats had cardiomyopathy diagnosed as moderate. The most severe change in the current study was one male in Group 4 with mild degeneration/necrosis. The incidence of spontaneous degeneration/necrosis in young male rats is highly variable. Jokinen et al (2005[2]) reported rates of up to 100% in 14-week studies conducted for the National Toxicology Program. In the same paper, they concluded that treatment-related cardiotoxicity was generally diffuse, rather than focal. In only one of the agents they reviewed was there a treatment-related increase in the focal lesion, and in that case, there was a significant increase in both incidence and severity.

The slight numerical increase in the focal myocardial degeneration/necrosis in the current study is considered to be a random spontaneous finding. In the prior 28 day study of ABC-123 (2012ABB), the incidence in control group ran as high as 40% (2/5 recovery control males). Additionally, the incidence of the change is well within historical control incidence reported in the published literature (up to 100% in Jokinen et al 2005[2]), and the one mild lesion noted in Group 4, is less severe than that seen in three control males in the 28 day study of ABC-123 conducted at the same laboratory.

There were no changes related to the administration of ABC-123 to Sprague-Dawley Rats for three months at doses of up to 2 mg/kg/day.

EPL

Additional Pages

- **Compliance Statement**
- **Quality Assurance Statement**
- **Signature Page**

8. COMPLIANCE STATEMENT

Client Name	XYZ, Inc.	EPL Principal Investigator	Dr. Jeffery Engelhardt
Client Study	2012ABC	EPL Pathologist	Dr. Peter C. Mann
Species	Rat	EPL Project Number	999-001
Study Title	A 3-Month Study of ABC-123 by Oral Gavage Administration in Sprague-Dawley Rats with a 28-Day Recovery Period		
Test Article	ABC-123		

The Histopathology portions of the above-referenced study were conducted in compliance with the Good Laboratory Practice regulations of the Food and Drug Administration (FDA) as stipulated by 21 CFR Part 58; the Japanese Ministry of Health, Labor, and Welfare (MHLW) Good Laboratory Practice Standards, Ordinance 21; the Organisation for Economic Cooperation and Development (OECD), ENV/MC/CHEM (98) 17; and all applicable amendments.

EPL Principal Investigator

9. QUALITY ASSURANCE STATEMENT

Study Title: A 3-Month Study of ABC-123 by Oral Gavage Administration in Sprague-Dawley Rats with a 28-Day Recovery Period

Client Study: 2012ABC EPL Principal Investigator: Dr. Jeffery Engelhardt

EPL Project Number: 999-001 EPL Pathologist: Dr. Peter C. Mann

The following aspects of this study were inspected by the Quality Assurance Unit of Experimental Pathology Laboratories, Inc. Dates inspections were performed and findings reported to the EPL Principal Investigator and Management are indicated below.

Area Inspected	Dates	
	Inspection	Reporting
EPL Project Sheets		
Project Setup		
Data Review		
Draft Pathology Report		
Final Pathology Report		

Date reported to Study Director/Management _____

Date of last quarterly facility inspection 11/10

_____ _____

EPL Quality Assurance Unit Date

Signature Page

10. SIGNATURE

Study Pathologist:

_____ _____

Peter C. Mann, DVM, Diplomate, ACVP
Senior Veterinary Pathologist
Experimental Pathology Laboratories, Inc.

Date

Tables

- Summary Tables
- Individual Animal Microscopic Findings
- Gross-Micro Correlation Table

Summary Tables

PATHOLOGY REPORT (DRAFT) PAGE : 1/ 4
SUMMARY TABLES

TEST ITEM : ABC-123 PATHOL. NO.: 90109 PCM
TEST SYSTEM : RAT, 92 Days, Oral gavage DATE : 23-DEC-10
SPONSOR : XYZ, Inc PathData@System V6.2d2

NUMBER OF ANIMALS WITH MICROSCOPIC FINDINGS BY ORGAN/GROUP/SEX
Necropsy Status: TERMINAL SACRIFICE GROUP (KO), Incl. Deaths

Sex		Males		Females	
Dose Group		1	4	1	4
No. Animals per Dose Group		10	11	10	10
ADRENAL GLANDS	No.Examined	10	11	10	10
	NAD	10	11	10	10
AORTA	No.Examined	10	11	10	10
	NAD	10	11	10	10
BONE MARROW, FEMUR	No.Examined	10	11	10	10
	NAD	10	10	10	10
- Malignant Lymphoma		-	1	-	-
BONE MARROW, STERNUM	No.Examined	10	11	10	10
	NAD	10	10	10	10
- Malignant Lymphoma		-	1	-	-
BONE, FEMUR	No.Examined	10	11	10	10
	NAD	10	10	10	10
- Malignant Lymphoma		-	1	-	-
BONE, STERNUM	No.Examined	10	11	10	10
	NAD	10	10	10	10
- Malignant Lymphoma		-	1	-	-
BRAIN	No.Examined	10	11	10	10
	NAD	10	11	10	10
CERVIX	No.Examined	-	-	10	10
	NAD	-	-	10	10
EPIDIDYMIDES	No.Examined	10	11	-	-
	NAD	9	10	-	-

Individual Animal Reports

12/28/10 DRAFT

PATHOLOGY REPORT (DRAFT) PAGE : 1/ 10
INDIVIDUAL ANIMAL DATA

TEST ITEM : ABC-123 PATHOL. NO.: 90109 PCM
TEST SYSTEM : RAT, 92 Days, Oral gavage DATE : 23-DEC-10
SPONSOR : XYZ, Inc PathData@System V6.2d2

TABLE OF INDIVIDUAL MICROSCOPIC FINDINGS (AOFT)
DOSE GROUP : 1, 0 mg/kg/day

ANIMAL NUMBER :	1001 MK0	1002 MK0	1003 MK0	1004 MK0	1005 MK0	1006 MK0	1007 MK0	1008 MK0	1009 MK0	1010 MK0
ADRENAL GLANDS	-	-	-	-	-	-	-	-	-	-
AORTA	-	-	-	-	-	-	-	-	-	-
BONE MARROW, FEMUR	-	-	-	-	-	-	-	-	-	-
BONE MARROW, STERNUM	-	-	-	-	-	-	-	-	-	-
BONE, FEMUR	-	-	-	-	-	-	-	-	-	-
BONE, STERNUM	-	-	-	-	-	-	-	-	-	-
BRAIN	-	-	-	-	-	-	-	-	-	-
EPIDIDYMIDES	-	-	+	-	-	-	-	-	-	-
- Aospermia	.	.	2.	.	.	.	.	.	.	.
- Immature Forms	.	.	P.	.	.	.	.	.	.	.
ESOPHAGUS	-	-	-	-	-	-	-	-	-	-
EYES	-	-	-	-	-	-	-	-	-	-
HARDERIAN GLANDS	-	-	-	-	-	-	-	-	-	-
HEART	+	-	-	-	+	-	-	-	+	-
- Degeneration/Necrosis; Myocyte; w/Mononuclear Inflammation	.	.	.	.	1.	.	.	.	1.	.
- Degeneration; Myocardium; Focal	1.	.	.	.	.	.	.	.	.	.
- Hypertrophy/Edema; Pericardium.	2.	.	.	.	.	.	.	.	.	.
- Infiltration; Mononuclear Cell; Adipose Tissue	1.	.	.	.	.	.	.	.	.	.
- Infiltration; Mononuclear Cell; Subepicardial; Focal	2.	.	.	.	.	.	.	.	.	.

Gross-micro Correlation Table

PATHOLOGY REPORT (DRAFT) PAGE : 1/ 3
SUMMARY TABLES

TEST ITEM : ABC-123 PATHOL. NO.: 90109 PCM
TEST SYSTEM : RAT, 92 Days, Oral gavage DATE : 23-DEC-10
SPONSOR : XYZ, Inc PathData@System V6.2d2

CORRELATION TABLE: NECROPSY - MICROSCOPY DOSE GROUP 1, MALE

NECROPSY OBSERVATION	CORRESPONDING MICROSCOPIC FINDING
ANIMAL NO: 1005	
INTESTINE-SMALL, JEJUNUM	
- 01: Diverticulum, single.	- No corresponding finding.
TESTES	
- 01: Nodule; soft; right; single: attached to the superior pole of the right testis, nodule has testis like texture and appearance.	- Infarct; Focal, unilateral, grade 5.

Appendices

Appendix 1
Abbreviations and Glossary

ACVP	American College of Veterinary Pathologists
DVM	Doctor of Veterinary Medicine
H&E	Hematoxylin and eosin

Summary

- It's not always about the science
  - Strict scientific discussion will not always do the job
    - Remains the foundation of all negotiations
    - Politics may drive final decisions
- If it is perceived to be bad, it is bad
  - Need to reassure the regulator that the test article will not cause harm
- Understand the point of view of the regulator

Summary

- The toxicology and pathology evaluations should ensure that compound-induced alterations are presented
  - Clearly
  - Consistently
  - Accurately
  - Understandably

- Importance of the findings for safety is explicitly identified for inclusion in the various regulatory documents

Conclusions

- Humans remain the ultimate test species for biopharmaceuticals
- Nonclinical studies only provide guidance for the physician
- Toxicities in animals may not translate directly to humans and vice versa
- Animal studies are not the ultimate source of data on side effect profile

If you would like a copy of this presentation and the pathology report template, please contact me at:

pmann@epl-inc.com