Pathology Findings in Pharmaceutical Development
Tips & Tricks

A summary of key messages from the first seminar in Basel, December 6th 2017

Introduction

- Anatomic pathology in nonclinical involves the examination of tissue sections from animal studies after administration of varying doses of the test compound.
  In clinical pathology, blood samples from human clinical studies or animals are analyzed.

- The following tips and tricks are extracted from presentations given by our pathologists Dr. Maurice Cary (anatomic pathology) and Dr. Barbara von Beust (clinical pathology). They are based on numerous cases from client companies.

Clinical and Nonclinical Experts

www.cn-experts.com

info@cn-experts.com

Anatomic Pathology

Situation #1:
The study report shows that the tox study is totally clean, i.e. there are no histopathology findings.

Tip: Make sure to check the exposure. If there are no findings, you may not have reached a sufficient level of exposure. FDA and EMA require that the toxicity is characterized, or that you show that there is maximum exposure to the tissue or organ examined.

Situation #2:
There is a finding in an animal study.

Tip: Consider whether this finding is relevant to human safety; e.g. is there is a counterpart to humans? Some findings are normal for the test species and should not be considered as a finding. An example of this is Extramedullary Hematopoiesis (EMH) in mice and rats, which is normal in adult mice and rats and has no human counterpart.

Situation #3:
The study report includes a long list of target organs.

Tip: Consider that this may be a sign of "overdiagnosis". Very few small molecules result in findings in multiple (5,6,7) organs.

Situation #4:
You observe vacuoles in brain neurons.

Tip: This may be an artefact. Brain-processing artefacts may appear if the tissue stays too long in alcohol, which may lead to vacuoles in neurons. If there is a hole (i.e. vacuole) in a neuron, there should be an associated reaction of some sort. If not, its an artefact. It's simple ☺

Situation #5:
You observe lesions in adrenal, lymph nodes, or bone tissue.

Tip: These tissues are prone to cutting or sectioning artefact. If the tissue is cut off-center, it can look like a finding. Bone/joint expertise is not common, so experts should be consulted in case of findings to reach the right conclusion.

Situation #6:
You work with a biologic and observe no relation of the findings to the dose.

Tip: You are probably dealing with an immunogenic reaction. Before concluding this, rule out that you might be looking at the pharmacologic effect or an off-target effect.

Clinical Pathology

Situation #1:
Blood data looks strange with no correlation between dose and effect.

Tip 1: Blood and its components is a very dynamic system. As opposed to a dead body/necropsy, blood continues to change after a sampling at any given time (and after death). Blood data reflect the moment and artefacts need to be considered at any time.

Tip 2: Be aware of artefacts due to frequent or excessive blood sampling, which could for example lead to "anemia" at the end of the study.

Tip 3: Standardization is important. You have to standardize pre-analytic aspects such as blood sampling (location, time, technique, frequency, total volume), randomization, storage, lag time and analytic aspects such as method and assay validation and quality control.

Situation #2:
You are considering to invest in a bone marrow analysis.

Tip: Bone marrow analysis is only necessary if there are findings in the hematology data. Too often, bone marrow analysis is performed before the hematology data are analyzed.

Situation #3:
You see changes in the hemogram (blood composition).

Tip: Always check back with the clinics for observations, food consumption, body weight gain, and ask the personnel if they saw something that can explain the changes. For example, increase in urea and creatinine, which is usually markers for renal insufficiency, could be caused by simple hemoconcentration effects and have nothing to do with renal toxicity or dysfunction.

Situation #4:
You are asked to quickly set up a new tox study.

Tip: Make sure that your instrument and method are validated before initiating any study. Many instruments are designed for human samples and clinical use and validation protocols are not always established in a particular laboratory. This increases the risk of producing invalid data.