The Toxicologic Pathologists - Their Role and Responsibilities During Drug Development – Challenges in Interpretation of Preclinical Safety Studies

Abraham Nyska, DVM, Diplomate ECVP, Fellow IATP
Expert in Toxicologic Pathology
Visiting Full Professor of Pathology
Sackler School of Medicine, Tel Aviv University
Haharuv 18, P.O.Box 184
Timrat, 36576; Israel
Cellphone: 054 300 3447
E mail: anyska@bezeqint.net
Website: http://www.nyska.net
OUTLINE OF THE LECTURE

• 1\textsuperscript{st} half - Role of \textbf{Toxicologic Pathologist} in drug development

• 2\textsuperscript{nd} half – Application of imaging technologies in Toxicologic Pathology – “\textit{The Magnetic Resonance Imaging (MRI) Histology = Smart sections}”
**Definition:** Investigation of structural and functional consequences of injurious stimuli (i.e., chemicals, drugs or physical agents)

The Discipline of Toxicologic Pathology
The Role of the Toxicologic Pathologist in the Biopharmaceutical Industry

Susan van Tongeren\textsuperscript{1}, Jane A. Fagerland\textsuperscript{2}, Michael W. Conner\textsuperscript{3}, Kelly Diegel\textsuperscript{4}, Kevin Donnelly\textsuperscript{5}, Branka Grubor\textsuperscript{6}, Alric Lopez-Martinez\textsuperscript{7}, Anne Provencher Bolliger\textsuperscript{8}, Alok Sharma\textsuperscript{9}, Sarah Tannehill-Gregg\textsuperscript{10}, Patricia V. Turner\textsuperscript{11} and Lyn M. Wancket\textsuperscript{12}

Abstract
Toxicologic pathologists contribute significantly to the development of new biopharmaceuticals, yet there is often a lack of awareness of this specialized role. As the members of multidisciplinary teams, toxicologic pathologists participate in all aspects of the drug development process. This review is part of an initiative by the Society of Toxicologic Pathology to educate scientists about toxicologic pathology and to attract junior scientists, veterinary students, and veterinarians into the field. We describe the role of toxicologic pathologists in identifying candidate agents, elucidating bioactive pathways, and evaluating efficacy and toxicity in preclinical animal models. Educational and specialized training requirements and the challenges of working in a global environment are discussed. The biopharmaceutical industry provides diverse, challenging, and rewarding career opportunities in toxicologic pathology. We hope that this review promotes understanding of the important role the toxicologic pathologist plays in drug development and encourages exploration of an important career option.
The Pivotal Role of the Toxicologist Pathologist in All Phases of Drug Development

Duration of Drug Development 8-15 Years

Clinical Trials
- Phase I
- Phase II
- Phase III

Non Clinical Studies
- Exploratory Studies
- Acute, Subacute Studies
- Chronic Studies

Toxicologic Pathologist

Drug Discovery

First Human Dose

Market Launch

Duration of Drug Development 8-15 Years

First Human Dose
The preclinical evaluation – What are the goals?

- Pre-clinical pharm/tox data are used to:
  - Identify target organs and make correct interpretation about their significance
  - Identify need for specialized clinical safety monitoring
  - Select starting doses/regimens
  - Estimate pharmacokinetics, i.e. investigate the relationship between exposure and toxicity

The purpose of animal (preclinical) safety studies is not to use it for direct extrapolation of animal data to humans. Rather, the goal is to use animal data to characterize potentially adverse changes that might be expected to occur in humans in response to administration of a particular drug and recommend the dose level that should be safe to start with.
Challenges in drug development - The importance of correct evaluation and interpretation of preclinical toxicity findings

- The successful navigation of a new molecule or chemical through the Discovery and Development process to market requires a series of carefully considered “GO, NO GO” decisions. Decisions related to toxicity issues that result in the unnecessary termination of a promising molecule are as unfortunate as allowing a potentially harmful molecule to progress.

- It is therefore pivotally important, using extensive investigation, experience and knowledge, to make a careful and integrated assessment of in-life, anatomic and clinical pathology findings derived from toxicity studies.
The optimal outcome of preclinical program…

- The **optimal goal - outcome** is to predict the preclinical long-term SAFETY OF THE DRUG from the 14 days and 3 months studies.
- The pharmaceutical companies are eager to predict unsafe drugs as early as possible, without wasting expensive resources, but on the other hand, not to lose good drugs that induce irrelevant pathology in preclinical program.
• Importance of much experienced director of R&D, known for exercising good judgment.

• Importance of location of the company headquarter, market size and therapeutic area.

• It is estimated that 90% of industry R&D expenditures now go into molecules that never reach the market. In this context, making the right decision on what to progress to late-stage clinical trials is paramount in driving productivity.

• According the Pfizer: ”about 2/3 of the phase I compounds could have been predicted to be likely failures on the basis of available data”.

• There is strong bias in most R&D organization in “progression seeking” behavior instead of “truth seeking” behavior (for reasons such as job-security, position in the organization and passion to the compound).
Histopathology –
*The Art of Vision and Description*
Microscopy Will Remain a Cornerstone of Surgical Pathology

Rosai J, Laboratory Investigation (2007) 87, 403–408
A “Pharmacological” (Adaptive) Effect in the Liver
Drug-induced target organ toxicity

Causes of Attrition of Pharmaceutical Candidates: The Opportunity

- ADME 9%
- Safety 44%
- Efficacy 28%
- Business 19%

Candidate Attrition Due to Toxicity: BMS Experience

Approximate Industry Standard

Year: 95, 96, 97, 98, 99, 00, 01, 02, 03, 04, 05, 06, 07
# Historic Causes of Attrition

All Therapeutic Areas

<table>
<thead>
<tr>
<th>Toxicity mechanism</th>
<th>%</th>
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<tbody>
<tr>
<td>Pharmacologic target-based</td>
<td>23.3</td>
</tr>
<tr>
<td>Biotransformation-related</td>
<td>21.9</td>
</tr>
<tr>
<td>Immune-mediated</td>
<td>11.0</td>
</tr>
<tr>
<td><strong>Target toxicity organ or tissue</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>27.4</td>
</tr>
<tr>
<td>Liver</td>
<td>11.0</td>
</tr>
<tr>
<td>Fetal tissues (teratogenicity)</td>
<td>9.6</td>
</tr>
<tr>
<td>Hematologic</td>
<td>8.2</td>
</tr>
<tr>
<td>CNS/PNS</td>
<td>8.2</td>
</tr>
<tr>
<td>Retina</td>
<td>6.8</td>
</tr>
<tr>
<td>Genotoxicity</td>
<td>5.5</td>
</tr>
<tr>
<td>GI, pancreas, testis, muscle, lung, carc, renal, acute</td>
<td></td>
</tr>
<tr>
<td>toxicity</td>
<td>&lt;4.1</td>
</tr>
</tbody>
</table>

* Total ≠ 100% due to overlapping categories multiple toxicities (Car BD. American Drug Discov, 1:53-56, 2006)
Liver section from a male mouse treated with 1 mg/kg Kawa Kawa for 2 years. Note (arrows), hepatoblastoma.

Other toxic lesions observed in the liver of Kawa Kawa treated mice:
* Hepatocytic fatty changes
* Cystic degeneration

Excellent predictive value of preclinical studies
Flu vaccine-induced pericarditis in mice

Case reports of post-flu vaccination of pericarditis


Excellent predictive value of preclinical studies
Opioid Neurotoxicity: Neuropathologic Effects in Rats of Different Fentanyl Congeners – Acute effect

- Hippocampal CA1 sector (rat) 24 hrs. after fentanyl treatment

(rats)

(H&E- vs. Fluoro-Jade B-stained sections)
Opioid Neurotoxicity: Neuropathologic Effects in Rats of Different Fentanyl Congeners – Chronic effect
Histopathological finding that may be of no relevance to human
HYALINE DROPLET NEPHROPATHY (MALLORY-HEIDENHAIN STAIN – MALE FISCHER 344 -O-NITROTOLUENE
The case of irrelevance of thyroid adenomas noted in rats treated with hepatic liver inducers of P450 enzymes
Treatment related thyroid hypertrophy, hyperplasia and adenoma secondary to liver microsomal induction

Control thyroid

Thyroid from a treated rat – follicular hypertrophic epithelium

Follicular cell adenoma
Qualitative and Quantitative Analysis of Nonneoplastic Lesions in Toxicology Studies

Cynthia Shackelford, Gerald Long, Jeffrey Wolf, Carlin Okerberg, and Ronald Herbert

1Experimental Pathology Laboratories, Inc, Research Triangle Park, North Carolina 27709
2Eli Lilly & Company Lilly Research Laboratories, Greenfield, Indiana, 46140, and
3National Institute for Environmental Health Sciences, Research Triangle Park, North Carolina, 27709
### Table 1.—Some commonly used severity grading schemes.

<table>
<thead>
<tr>
<th>Grading scheme I</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = Not present</td>
<td>(&lt; 10%)</td>
<td>(0–25%)</td>
</tr>
<tr>
<td>1 = Minimal</td>
<td>(10–39%)</td>
<td>(26–50%)</td>
</tr>
<tr>
<td>2 = Slight</td>
<td>(40–79%)</td>
<td>(51–75%)</td>
</tr>
<tr>
<td>3 = Moderate</td>
<td>(80–100%)</td>
<td>(76–100%)</td>
</tr>
<tr>
<td>4 = Moderately Severe/high</td>
<td>(51–75%)</td>
<td></td>
</tr>
<tr>
<td>5 = Severe/high</td>
<td>(76–100%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Grading scheme II</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 = Minimal</td>
<td>(&lt; 10%)</td>
<td>(0–25%)</td>
</tr>
<tr>
<td>Grade 2 = Mild</td>
<td>(10–39%)</td>
<td>(26–50%)</td>
</tr>
<tr>
<td>Grade 3 = Moderate</td>
<td>(40–79%)</td>
<td>(51–75%)</td>
</tr>
<tr>
<td>Grade 4 = Marked</td>
<td>(80–100%)</td>
<td>(76–100%)</td>
</tr>
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</table>

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<tr>
<th>Grading scheme III</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 = Minimal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2 = Slight</td>
<td>(same as mild)</td>
<td></td>
</tr>
<tr>
<td>Grade 3 = Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 = Marked</td>
<td>(same as severe)</td>
<td></td>
</tr>
<tr>
<td>Grade 5 = Massive</td>
<td>(same as very severe)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2.—Severity grading scheme criteria for various organs.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (+1): Minimal</td>
<td>This corresponds to a histologic change that may be barely noticeable to changes considered so minor, small, or infrequent as to warrant no more than the least assignable grade (0–10%). For focal, multifocal or diffusely distributed lesions, this grade is used for processes where &lt; 10% of the tissue is involved. For hyperplastic/hypoplastic/atrophic lesions, this grade is used when the affected structure or tissue has undergone &lt; 10% increase or decrease in volume.</td>
<td></td>
</tr>
<tr>
<td>2 (+2): Mild</td>
<td>This corresponds to a histologic change that is a noticeable but not a prominent feature of the tissue. For focal, multifocal or diffusely distributed lesions, this grade is used for processes where between 11–20% of the tissue is involved. For hyperplastic/hypoplastic/atrophic lesions, this grade is used when the affected structure or tissue has undergone between an 11% and 20% increase or decrease in volume.</td>
<td></td>
</tr>
<tr>
<td>3 (+3): Moderate</td>
<td>This corresponds to a histologic change that is a prominent feature of the tissue. For focal, multifocal or diffusely distributed lesions, this grade is used for processes where 21–40% of the tissue section is involved. For hyperplastic/hypoplastic/atrophic lesions, this grade is used when the affected structure or tissue has undergone between a 21% and 40% increase or decrease in volume.</td>
<td></td>
</tr>
<tr>
<td>4 (+4): Marked</td>
<td>This corresponds to a histologic change that is an overwhelming feature of the tissue. For focal, multifocal or diffusely distributed lesions, this grade is used for processes where 41–100% of the tissue section is involved. For hyperplastic/hypoplastic/atrophic lesions, this grade is used when the affected structure or tissue has undergone between a 41% and 100% increase or decrease in volume.</td>
<td></td>
</tr>
</tbody>
</table>
Histopathology raw data

- The signed final pathology report, representing the consensus of the primary and peer review pathologists
- Slides, tissues, paraffin blocks, and slides
Revised guides for organ sampling and trimming in rats and mice – Part 2

A joint publication of the RITA*) and NACAD**) groups

Birgit Kittel1, Christine Ruehl-Fehlert2, Gerd Morawietz3, Jan Klapwijk4, Michael R. Elwell5, Barbara Lenz6, M. Gerard O’Sullivan7, Daniel R. Roth8, and Peter F. Wadsworth9

With 65 figures

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Address for correspondence: Gerd Morawietz, Department of Information Technology and Databases, Fraunhofer Institute of Toxicology and Experimental Medicine, Nikolai-Fuchs-Str. 1, 30625 Hannover, Germany; Fax: ++49 511 5350 155, E-mail: morawietz@itcm.fraunhofer.de

Key words: Trimming; RITA; NACAD; rat; mouse; standardization; guidelines; nasal cavity; nasopharynx; paranasal sinuses; larynx; trachea; bronchi; bronchiole; lung; testes; rete testis; epididymis; prostate; coagulating gland; seminal vesicle; ovary; oviduct; uterus; uterine cervix; vagina; pituitary gland; thyroid gland; parathyroid gland; adrenal gland.

*) RITA: Registry of Industrial Toxicology Animal-data. Members: Abbott GmbH & Co KG, Ludwigshafen, Germany; ALTANA Pharma AG, Hamburg, Germany; AstraZeneca, Södertälje, Sweden and Macclesfield, England; Aventis Pharma Deutschland GmbH, Hattersheim, Germany; BASF AG, Ludwigshafen, Germany; Bayer HealthCare AG, Wuppertal, Germany; Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany; Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany; Hoffman-LaRoche AG, Basel, Switzerland; Meck KGaA, Darmstadt, Germany; Novartis Pharma AG, Basel, Switzerland; Pfizer, Amboise, France; Pharmacia, Nerviano, Italy; Syngenta CTL, Macclesfield, England

**) NACAD: North American Control Animal Database. Members: 3M Pharmaceuticals, St. Paul, MN, USA; Adolor Corporation, Malvern, PA, USA; Bayer CropScience, Stillwell, KS, USA; Pfizer, Inc., Groton, CT, USA; Pfizer, Inc., Ann Arbor, MI, USA; Pharmacia, Inc., Kalamazoo, MI, USA; R.W. Johnson Pharmaceutical Research Institute, Spring House, PA, USA; Schering-Plough Research Institute, Lafayette, NJ, USA

Summary
This is the second part of a series of three articles on trimming instructions of rat and mouse protocol organs and tissues in regulatory toxicology studies, covering the respiratory, male and female genital, and the endocrine systems. The article is based on the experience of the European RITA and American NACAD working groups and is an extended revision of trimming guides published in 1995 (BAHNEMANN et al.). The optimum localization for tissue preparation, the sample size, the direction of sectioning and the number of sections to be prepared is described organ by organ. These descriptions are illustrated for each organ by a schematic drawing and/or a macro-photograph showing the plane of section as well as a low magnification of the H&E stained slide demonstrating the optimum "end-product".

The objectives of this work, as addressed in detail in the first part (RUEHL-FEHLERT et al. 2003), are to stan-
4 Male genital system

4.4 Prostate

Localization: Dorsolateral and ventral lobe
Number of sections: 1
Direction: Longitudinal horizontal after special preparation (see below).

Fig. 4.4a. Prostate, rat, ventral aspect. Lateral lobes not visible, dorsal lobe: only caudal part visible.

Fig. 4.4b. Prostate, rat, dorsal aspect.

The dorsolateral and ventral lobes that normally lie in a vertical axis above each other (with urinary bladder and seminal vesicles in between) are spread in a horizontal axis and embedded with the “outer” aspect down into the cassette.

Preparation: The group of adjacent organs consisting of prostate, urinary bladder, seminal vesicles and coagulation glands is removed (see figures 4.4d through 4.4f) and (if weights are not required) fixed in situ to prevent leakage of the glandular secretions.

After fixation, the ventral lobe is detached from the urinary bladder and is flipped back. The urinary bladder and seminal vesicles with coagulation glands are removed. The two ventral lobes are separated from each other, but are left attached to the dorsolateral parts. The dissected prostate is put into a cassette with the “outer” surfaces down; i.e., ventral face of the ventral lobes down and dorsal face of the dorsolateral lobes down (see figures 4.4g through 4.4i). After histotechnical processing, a section at the mid level of the ventral lobes is made.

The dorsocranial lobe of the prostate (i.e., coagulating gland) is processed with the seminal vesicle.

Chemically induced or spontaneous proliferative lesions of the rat prostate can be found in all three lobes. The dorsal and lateral lobes exhibit the same spectrum of proliferative lesions. These differ from spontaneous and induced lesions in the ventral lobe. Additionally, some strain-specific deviations in the interlobular distribution of benign and malignant neoplasms consequently require the assessment of all compartments. Accordingly, a longitudinal-horizontal section through the prostate complex, including dorsolateral and ventral lobes, urethra and, optionally, ureter and ductus deferens represents a less time-consuming method, applicable to routine histological processing and examination.

Related references

Fig. 4.4c. Prostate.

Abbreviations used in figures 4.4c to 4.4b:
Cr: Coagulation gland
Dd: Ductus deferens
Dl: Dorsolateral lobe of prostate
Sv: Duct of seminal vesicle
Vl: Ventral lobe of prostate
Trimming of the liver

2 Digestive system
2.7 Liver and Gall bladder (mouse only)

Localization:
1) Left lateral lobe
2a) Rat: right medial lobe
2b) Mouse: left and right medial lobe including gall bladder
3) Optional: caudate lobe

Number of sections:
2 (3)

Direction:
1, 2a, 3) Transverse,
2b) longitudinal-vertical

Remarks:
Sample sizes should be as large as possible but can be adapted so that all pieces fit into one cassette. For identification purposes, standardized shaping of one of the larger lobes can be performed.

Fig. 2.7a. Liver, visceral aspect, indicating the cut levels for rats and mice.

Fig. 2.7b. Rat liver, visceral aspect.

Fig. 2.7d. Mouse: liver and gall bladder (G), sections 1 and 2b.
Society of Toxicologic Pathology
Recommendations

Toxicologic Pathology, 32:269–270, 2004
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DOI: 10.1080/01926230490274443

Recommendations to Guide Determining Cause of Death in Toxicity Studies
The pathologist is responsible for identifying the cause of death (COD) and/or morbidity in animals that die or are euthanized prior to scheduled necropsy in toxicology studies, including carcinogenicity studies.

The COD may not be the proximate event leading to death, but **should be the overall process** that leads to the proximate cause.
The pathologist should have and use all available information for each animal to determine the COD. This includes data such as hematology, clinical chemistry, body weights, clinical observations, metabolism, etc.

The pathologist should determine whether overall mortality and any differences in mortality among groups are the result of compound administration.

If the COD cannot be determined, this should be stated as COD undetermined or COD not determined from the available information.
The purpose of the peer review process is to ensure the pathology report is an accurate reflection of the pathology findings for the study....
A Commentary on the Process of Peer Review and Pathology Data Locking

Jennifer S. McKay,1,* Erio Barale-Thomas,2 Brad Bolon,3 Catherine George,4,* Jerry Hardisty,5 Sunao Manabe,6,* Frederic Schorsch,7,* Munehiro Teranishi,6 and Klaus Weber8

1AstraZeneca, Macclesfield, SK10 4TG, United Kingdom
2Johnson and Johnson PRD, 2340 Beersel, Belgium
3GEMpath Inc., Longmont, CO 80503-2339, USA
4Ipsen, 91966 Les Ulis Cedex, France
5Experimental Pathology Laboratories, Research Triangle Park NC 22709, USA
6Daichi Sankyo Co., Ltd., Japan
7Bayer CropScience, 69009 Lyon, France
8Harlan Laboratories, 4452 Itingen, Switzerland

In conclusion, for the reasons outlined above and in accordance with current U.S. and European guideline recommendations on pathology peer review, we support the JSTP in their pursuit of a revised Japanese pathology peer-review guideline (1) allowing sponsor peer review prior to locking of pathology data and (2) acknowledging that interim worksheets are not raw data and therefore do not need to be retained or submitted.
Recommendations for Pathology Peer Review

Daniel Morton\(^1\), Rani S. Sellers\(^2\), Ernio Barale-Thomas\(^3\), Brad Bolon\(^4\), Catherine George\(^5\), Jerry F. Hardisty\(^6\), Armando Irizarry\(^7\), Jennifer S. McKay\(^8\), Marielle Odin\(^9\), and Munehiro Teranishi\(^10\)

\(^1\)Pfizer Inc., Groton, Connecticut, USA  
\(^2\)Albert Einstein College of Medicine, Bronx, New York, USA  
\(^3\)Johnson & Johnson, Beerse, Belgium  
\(^4\)GEMpath, Longmont, Colorado, USA  
\(^5\)IPSEN Innovation ZA, Les Ulis, France  
\(^6\)Experimental Pathology Laboratories, Inc., Sterling, Virginia, USA  
\(^7\)Eli Lilly & Company, Indianapolis, Indiana, USA  
\(^8\)AstraZeneca Pharmaceuticals LP, Cheshire, UK  
\(^9\)Roche Pharma, Nutley, New Jersey, USA  
\(^10\)Daiichi Sankyo Co., Ltd., Shizuoka, Japan

Abstract

Pathology peer review verifies and improves the accuracy and quality of pathology diagnoses and interpretations. Pathology peer review is recommended when important risk assessment or business decisions are based on nonclinical studies. For pathology peer review conducted before study completion, the peer-review pathologist reviews sufficient slides and pathology data to assist the study pathologist in refining pathology diagnoses and interpretations. Materials to be reviewed are selected by the peer-review pathologist. Consultations with additional experts or a formal (documented) pathology working group may be used to resolve discrepancies. The study pathologist is solely responsible for the content of the final pathology data and report, makes changes resulting from peer-review discussions, initiates the audit trail for microscopic observations after all changes resulting from peer-review have been made, and signs the final pathologist’s report. The peer-review pathologist creates a signed peer-review memo describing the peer-review process and confirming that the study pathologist’s report accurately and appropriately reflects the pathology data. The study pathologist also may sign a statement of consensus. It is not necessary to archive working notes created during the peer-review process.
DRAFT OECD guidance document on pathology peer review

- Records and reporting of the peer review should be sufficiently detailed to allow reconstruction of the process and verification that the correct tissues were examined.
- The GLP compliance status of the peer review should be clearly stated in the final report.
Scanning of the slides on the web – Aperio – Leica system
The incoming “future” of the peer review
I SAID ‘SPINDLE CELL’ AND HE SAID ‘SQUAMOUS CELL’

SO WHAT DID YOU SAY THEN?

WELL, THEN I HAD TO KICK HIS ASS.
The New Nomenclature Project
INHAND

International Harmonization of Nomenclature
and Diagnostic Criteria for Lesions in Rats and Mice
Objectives of the INHAND

• Established at 2006, as a joint initiatives of the American, Japanese, European Societies of Toxicologic Pathology

• To produce publications for each organ system that provide a standardized nomenclature and differential diagnosis for classifying microscopic lesions observed in laboratory rats and mice in toxicity and carcinogenicity studies.

• To serve in advisory role for the FDA SEND initiative with the goal of mapping INHAND terminology to SEND codelists of preferred terms
Structure of the INHAND Organization

• Management by a Global Executive Steering Committee (**GESC**) with representation from major societies of toxicologic pathology

• Composed of 15 organ system working groups (**OWG**) defined by the GESC (dealing with **rodents** only)

• 4 **non rodent** species working groups to be formed
# Descriptive vs. Interpretative Terms

<table>
<thead>
<tr>
<th>Descriptive (preferred)</th>
<th>Interpretative (not recommended)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased cells</td>
<td>Atrophy&lt;br&gt;Lymphoid depletion&lt;br&gt;Involution&lt;br&gt;Hypoplasia</td>
</tr>
<tr>
<td>Increased cells</td>
<td>Hypertrophy&lt;br&gt;Hyperplasia&lt;br&gt;Proliferation</td>
</tr>
</tbody>
</table>

**EXAMPLE:** Recommended Terminology for Immunopathologic (i.e., Immunotoxic) Treatment-related Findings
Thymus

Drug Induced Decreased Thickness of the Cortex, Due to Decreased Number of Lymphocytes

Control Animal
No abnormality detected

Treated Animal
Cortex – Lymphocytes, decreased Cellularity, moderate
Proliferative and Nonproliferative Lesions of the Rat and Mouse Hepatobiliary System

Toxicologic Pathology, 38: 5S-81S, 2010
INHAND Collaboration with the FDA on SEND (Standard for the Exchange of Nonclinical Data)

Background:

• During 2011, the INHAND Global Editorial Steering Committee (GESC) had discussions with representatives of FDA Center for Drug Evaluation and Research (CDER) and members of the Clinical Data Interchange Standards Consortium (CDISC) to examine the potential use of INHAND terminology in the software being developed for Standard for Exchange of Nonclinical Data (SEND) submission to the FDA.

• The decision of the Government and industry toxicologists is that SEND terminology will widely accept the INHAND nomenclature.
Summary – Benefits

• Standardized submitted data will result in submission efficiencies such as providing one standard used by sponsors and vendors, reduce review time, and increase reviewer efficiency.

• Electronically submitted data for drug development program, when submitted in standardized format, can be searched within a study, across studies within a program, or across different programs.

• It will allow reviewers to communicate their questions more precisely to the sponsor.

References and presentation can be submitted upon demand – anyska@bezeqint.net
Challenges in Interpretation of Pre-clinical Histopathological Data
It is All a Matter of Right Interpretation…
Intramyocardial Injected “Drug” (Considered A Medical Device) Contaminated by Foreign Material, Provoking Granulomatous Reaction
A Drug “Contaminated” with Gauze – Cotton Fiber

Foreign Body Coronary Arteritis

Hematoxylin and Eosin

Polarizing Microscope
Issue of Hepatic Centrilobular Bridging Fibrosis Observed in Dermal Toxicity Studies

Drug administered by the subcutaneous route

Liver

Injection Site
26 Weeks Dermal Toxicity Study in Rat – Centrilobular Hepatic Fibrosis

Arrows – Centrilobular fibrosis
The Liver Acinus

**FIGURE 17.6**

*The liver acinus.* The liver acinus is a functional interpretation of liver organization. It consists of adjacent sectors of neighboring hexagonal fields of classic lobules partially separated by distributing blood vessels. The zones, marked 1, 2, and 3, are supplied with blood that is most oxygenated and richest in nutrients in zone 1 and least so in zone 3. The terminal hepatic venules (central veins) in this interpretation are at the edges of the acinus instead of in the center, as in the classic lobule. The vessels of the portal canals, namely, terminal branches of the portal vein and hepatic artery that, along with the smallest bile ducts, make up the portal triad, are shown at the corners of the hexagon that outlines the cross-sectioned profile of the classic lobule.
Injection Site – 13 Weeks Dermal Toxicity Study –
Cavity formation Surrounded by Necrosis (black arrows) and Bacterial colonies (red arrows)

Central cavity of drug deposition

Arrows – Necrosis
Injection Site – 13 Weeks Dermal Toxicity Study – Cavity formation Surrounded by Necrosis and Chronic Inflammation (black arrows)

- Injection site necrosis and fibrosis
- Central cavity of drug deposition
“Focal or multifocal hepatic necrosis, known as "corset liver", was seen in women in times when severely stringent corsets were fashionable… The lesion was presumably due to interference with vascular perfusion in compressed areas of the liver and may be similar to the hepatic lesions observed in our work”…

Rodent Cases of Liver Necrosis and Fibrosis in Comparable Circumstances…

- The long-term wrapping of the animal caused constriction and physical compression of the abdomen

- Hepatic centrilobular degeneration and fibrosis were attributed to passive congestion… rats that died during the course of the study had severe hepatic congestion and dilated cardiac ventricles, which were attributed to cardiac or respiratory failure due to pressure exerted by the wrap

Dermal Toxicity Studies: Factors Impacting Study Interpretation and Outcome

SUNDEEP A. CHANDRA¹, ALAN H. STOKES¹, RICK HALEY¹, CHRISTINE L. MERRILL¹, DAVID H. MELICH¹, KRISTINA DESMET¹, SYLVIA M. FURST¹, RICHARD A. PETERSON¹, KATHERINE MELLON-KUSIBAB¹, AND RICK R. ADLER¹

¹Safety Assessment, GlaxoSmithKline, Research Triangle Park, North Carolina, USA

ABSTRACT

The field of dermal toxicity continues to evolve in order to accurately predict dermal (and systemic) responses in humans to topically applied chemicals. Although the testing methods have undergone extensive refinements, idiosyncrasies and unexpected issues during the conduct of these studies are not unusual due to the plethora of new vehicles available for formulating test substances, changing regulatory requirements, and introducing new strain and/or species of laboratory animals as no single species or method seems to suffice for evaluating skin toxicity. The objective of this article is to illustrate some pragmatic issues that should be considered during the conduct as well as interpretation of dermal toxicity studies. Routine procedure-related issues such as hair clipping, tape stripping, and wrapping the animal’s torso to prevent oral ingestion can influence the interpretation. Excipients used in dermal toxicity studies may be nontoxic when used alone but complex dermal formulations can result in unexpected irritation and toxicity. In conclusion, interpretation and risk assessment of dermal toxicity studies should be done in a comprehensive manner, taking into account procedure-related impact on study results, unique species susceptibility, limitation of gross visual (naked eye) observation for evidence of toxicity, and normal anatomical variation.
Dermal Toxicity Studies: Factors Impacting Study Interpretation and Outcome

**Wrapping Procedure**

**Figure 2.**—Hepatocellular necrosis in rabbits associated with wrapping the torso. The changes are characterized by bridging coagulative necrosis affecting some portions of a lobe while sparing other regions (A and B). Discrete subcapsular area of necrosis (C) sparing the portal areas (D). HE.
LESIONS RELATED TO IV ROUTE OF ADMINISTRATION
- TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD

• A range of lesions were seen at the local implantation and injection site, in the heart, aorta, and lungs, resulted from the catheter used for the drug administration, introduced through the right jugular vein.

• Such changes included: capsule formation at the implantation site, inflammation in the jugular vein and subcutis, presence of singular organized thrombi in the lungs and a single case of minimal focal inflammation in the heart and aorta.

• In particular, a single male animal from group 4 had minimal centrilobular vacuolation, associated with single cell hepatocytic cell necrosis. This change is considered to reflect systemic circulatory problem, secondary to focal heart inflammation seen in this animal, provoked by the introduction of the catheter.
26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – JUGULAR VEIN THROMBOSIS

Detachment of fragments from the jugular vein thrombosis, leading to pulmonary thrombosis
LESIONS RELATED TO IV ROUTE OF ADMINISTRATION–
26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY
PERIOD - LUNG THROMBOSIS (different grades of vascular obstruction)
26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – AORTA – AN ABCESS (DUE TO TRAUMATIC LESION BY THE CATHETER)
26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – HEART – BACTERIAL VALVULAR ENDOCARDITIS (DUE TO TRAUMATIC LESION BY THE CATHETER)

Severe heart pathology leading to congestive heart failure with hepatic centrilobular congestion
Heart pathology leading to congestive heart failure with hepatic centrilobular degeneration and necrosis.
26 WEEK I.V. TOX STUDY IN MINIPIGS FOLLOWED BY A 6 WEEK RECOVERY PERIOD - LESIONS RELATED TO IV ROUTE OF ADMINISTRATION – CENTRIOLOBULAR HEPATOCYTIC DEGENERATION AND NECROSIS (APOPTOSIS) - this lesion is reflecting systemic circulatory stasis due to congestive heart failure

Same animal as the previous photo of focal myocarditis
END 1ST PART
Flowers in the Desert of Negev