CONTINUING EDUCATION IN TOXICOLOGIC PATHOLOGY
RESPIRATORY AND CARDIOVASCULAR SYSTEM

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REVIEW OF PATHOLOGY DATA FOR REGULATORY PURPOSES

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Agenda

- Introduction
- Background & overview of FDA's food additive approval process
- Pathology review process
- Common pathology review problems
- Recommendations for submitting pathology data
- Pathology review examples
- Conclusion

Introduction
FDA organization

- OC – Office of the Commissioner
- OCC – Office of the Chief Counsel
- ORA – Office of Regulatory Affairs
- CDER – Center for Drug Evaluation and Research
- CBER – Center for Biologics Evaluation and Research
- CDRH – Center for Devices and Radiological Research
- CVM – Center for Veterinary Medicine
- CFSAN – Center for Food Safety and Applied Nutrition
- CTP – Center for Tobacco Products
- NCTR – National Center for Toxicology Research

Background & Overview of FDA's Approval Process

Pertinent Laws and Regulations

- Federal Food, Drug and Cosmetic Act (1906)
  - Amendment: 1958, Food Additives
  - Amendment: 1960, Color Additives
    - Regulatory requirements similar for food and color additives
    - Strict Mandatory Safety Standards
      - New Additives unsafe until proven "safe" based on scientific studies
    - Burden of proof of safety with the petitioner

Background & Overview of FDA's Approval Process

Pertinent Definitions

Food Additive

❖"Direct" Food Additives

Section 201 (s) of FD&C Act defines… any substance, the intended use of which results or maybe expected to result, directly or indirectly in its becoming a component or otherwise affecting the characteristics of any food….

if such substance is not generally recognized among experts qualified by scientific training and experience….to be safe under the conditions of intended use

GRAS Exemption to food additive definition to exempt foods that are generally recognized as safe

Background & Overview of FDA's Approval Process

Pertinent Definitions (cont..)

Food Additive

❖"Indirect" Food Additives

Section 201 (s) of FD&C Act also includes indirect food additives or substances in contact with food (for example through food packaging), unintentional migration into food

Although "indirect" the 1958 Act treated them as food additives requiring complete filing with required animal studies/review/approval

Background & Overview of FDA's Approval Process
Premarket Approval Process (Indirect & GRAS)

1997 FDAMA established a premarket notification program for **indirect additives (food contact substances) and GRAS** substances

- Company notifies FDA 120 days prior to marketing
- Go to market if no FDA objection

FDA still requires premarket notification product uses contain the same quality / quantity of information applicable to all additives

Background & Overview of FDA's Approval Process

Delaney Clause; Constituent Policy

❖ Delaney Clause, 1958

- Explicitly "prohibits the approval of any additives shown to cause cancer in man or animals"
- No additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal…"

>absolute safety vs. reasonable certainty of no harm<

❖ Constituent Policy, 1982

- Impurities (For example, FDA approved permanent listing D&C Green #6, even though it contains the carcinogenic impurity, para-toluidine

Background & Overview of FDA's Approval Process

Pertinent Requirements

- Requirements include:
  - Chemistry data – chemical identity / purity
  - Environmental effects
  - Petition contains relevant safety data/animal studies such as: genetic toxicity, metabolism and pharmacokinetic studies, short term toxicity tests in rodents, sub-chronic toxicity tests with rodents and non-rodents, reproduction studies with a teratology phase, one year toxicity tests with non-rodent, chronic 18/24 month toxicity and carcinogenicity studies with rodents

Reference:

FDA's Red Book: Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food, Center for Food Safety and Applied Nutrition, US FDA

Background & Overview of FDA's Approval Process
Safety Assessment Considerations

- Estimated Daily Intake (EDI): probable dietary intake levels of the additive from its use in food
- Acceptable Daily Intake (ADI): intake level in humans that may be safely consumed by any member of the population without health or safety concerns
  - Usually derived from animal feeding studies: adverse effects and confirmed exposure levels associated with no adverse effects
- Safety Factor: 100 fold
  - 10 fold to account for the fact that data were obtained from feeding studies in animals
  - 10 fold to account for normal genetic variation / range of susceptibilities across human population
- Quantitative Risk Assessment
- Carcinogenic Risk Assessment (when additive contains carcinogenic contaminant, FDA uses constituent policy

Background & Overview of FDA's Approval Process

Approval Workflow

- Petition is received by FDA
- FDA's Consumer Safety Officer(s) (CSO) review for regulatory compliance and initiates scientific review
- Scientific team (chemists, mathematicians, pathologists, toxicologists etc.) reviews petition and provides recommendation
  - Cancer Assessment Committee
  - Quantitative Risk Assessment Committee
- Senior Management Review
- FDA Commissioner determines final rule
- Agency establishes a regulation (may or may not be in accordance with the use initially proposed by petitioner; may add conditions)
- Final Rule is published in the Federal Register and represents thorough scientific analysis and basis of decision

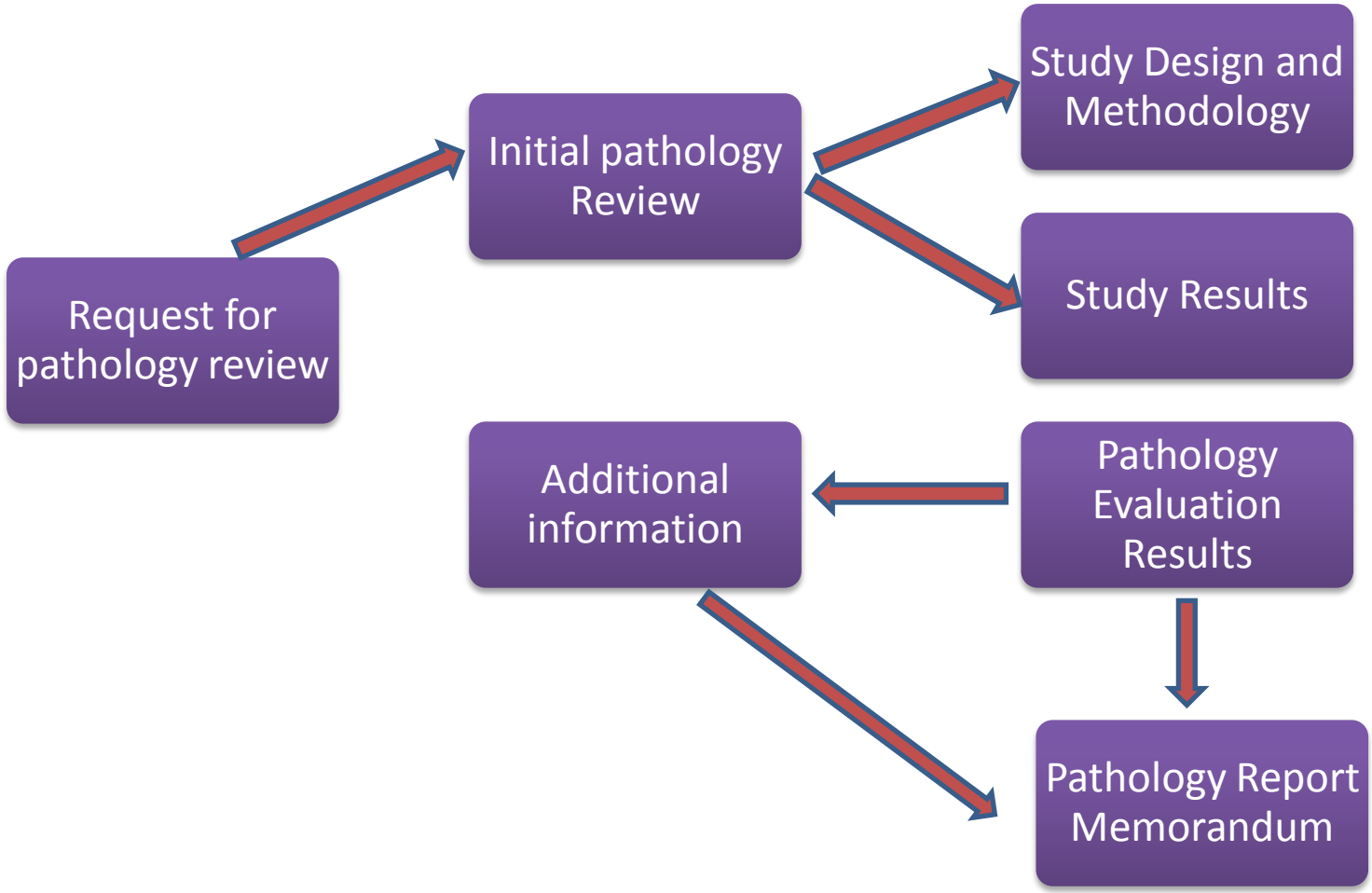
Pathology Review Process
Examination and Review of Pathology Data

Written Pathology Report

- Narrative
- Summary Tables
- Individual Animal Data
- Conclusions of the report

Pathology Review Process

Overall Review Workflow



Pathology Review Process
Examination of Pathology Data

Study Design and Methodology

- Animals: species, sex, strain, age
- Test article: mode of administration, treatment groups
- Animals per group, total number in the study
- Intended duration of the study, scope, and type of in-life study
- Interim sacrifices, recovery studies
- Scope of Post Mortem evaluation – gross, histopathology, fixatives and special stains

Pathology Review Process
Examination of Pathology Data

Results

- Survival pattern of the treated and control group animals
  - Number of animals alive at termination
  - Number of animals sacrificed moribund
- General health of the animals during the study
  - Outbreak of any disease

Pathology Review Process

Examination of Pathology Data

Results Cont….

- Body weight/food consumption
- Clinical and hematological findings
- Basis of incidence calculations
- Correlation of gross and microscopic findings
- Adequate description of gross and microscopic changes
- Diagnostic terminology

Pathology Review Process

Pathology Review Memorandum

- Pathology Review Memorandum includes:
  - Assessment of pathology findings
  - Adequacy of the qualitative / quantitative descriptions of lesions
  - Discussion of significance of findings / hazard identification for risk assessment
  - Recommendations for follow up data, if needed

Pathology Review Process

Follow Up Requests to complete Review

- Request for additional data / historical control data on specific lesions
- Request for additional slides, e.g. re-cuts and special stains
- Clarification of diagnostic criteria
- Micro slide review by FDA / independent characterization and verification of finding

Common Pathology Review Problems

- Missing / inaccurate / incomplete information
- Lack of adequate morphological descriptions and severity of lesions
- Inconsistent terminology for the same diagnosis
  - For example: c-cell / light cell / clear cell / parafollicular cell
- Inconsistency of multiple pathologists' terminology
- Failure of correlation of gross with histological findings
- Inaccurate summary numbers and summary tables
- Failure to describe the significance of findings
  - Treatment or experimental design related
  - Biological significance

Recommendations for Submitting Pathology Data

- Experimental design and methodology
  - Protocol issues should be addressed
- Presentation of data
  - Summary tables
  - Morphologic diagnosis – current
  - Lesion severity
  - Paired organs – unilateral / bilateral
  - Animal disposition table
- Pathologist's narrative
- Refer to FDA's Red Book for details

Pathology Review Examples

- Unique issues that required additional data to be resolved
  - Examples
    - FD&C Blue No. 2
    - Selected miscellaneous reviews of color additives
    - Liver data evaluations
    - Olestra
    - t-Butyl alcohol

Pathology Review Examples
FD & C Blue #2: Submitted Data

- Brain gliomas in male rats (two controls and three treated groups),
- 70/group: 0, 2, 1, 2, 6

Sponsor's initial submission: "the result of postmortem morphological examination revealed a statistically and biologically significant difference in the incidence of brain neoplasms"

Pathology Review Examples

FD & C Blue #2: Glioma Incidence

Group	Treatment	Glioma
1	Control	0/70 (0%)
2	Control	2/70 (2.9%)
3	Low dose	1/70 (1.4%)
4	Medium dose	2/70 (2.9%)
5	High dose	6/71 (8.4%)

Historical Controls: 3/585 (0.5%)

Pathology Review Examples
FD & C Blue #2: FDA Pathology Review

- Chronic rat study
  - Gliomas
  - No descriptive information
  - No definition of type of glioma
- Additional information?
  - Size, location, predominant cell type
- Further Studies
  - Additional Sectioning Requested

Pathology Review Examples
FD & C Blue #2: FDA Pathology Review

- **Results of Additional Sectioning/Review:**
  - Majority were astrocytomas, small, well differentiated
  - Re-cuts showed 4 more gliomas (male), 2 controls
  - Gliomas not seen grossly
  - No qualitative/morphologic differences
  - No multiple tumor formations
  - No gliosis
  - No invasiveness
  - No anaplasia
  - No treatment effect in females
  - Another contemporary control group in the same lab (6/70)

Pathology Review Examples

FD & C Blue #2: Pathology Conclusions

- Sponsor's Initial conclusion
  - Treatment related effect in male rats - glioma
  - No descriptive information
  - No definition of type of glioma
- FDA Review
  - Majority were astrocytomas, small, well differentiated
  - Seen in controls – lesions unrelated to treatment
  - FDA Conclusion: no treatment effect

Pathology Review Examples
FD & C Blue #2: FDA Final Review & Actions

- Cancer Assessment Committee (CAC)
- External Peer Review
- Legal Hearings
  - Brain tumors in male rats
  - Urinary bladder lesions in male rats
- Final Action

Pathology Review Examples

Selected Miscellaneous Color Additive Reviews

- FD&C Green #3:
  - Urinary bladder lesions
- FD&C Yellow #6:
  - kidney tumors
    - Additional sectioning
- FD&C Green #5:
  - Liver issues
- D&C Red #9 and Aniline type colors
  - Splenic fibrosis / fibroma / fibrosarcoma

Pathology Review Examples
Liver Data Evaluation
Antibacterial Agent in Adhesive Formulations

Liver lesions in mice (50/group) as presented in the **petitioner's report** (0, 20, 50, 150 mg/kg/day)

- **Males-**
  - Clear cell focus 1, 1, 1, 0
  - Focal hepatocytic hyperplasia 1, 8, 6, 1
  - Hepatocytic adenoma 4, 3, 5, 11*
  - Hepatocytic carcinoma 3, 3, 3, 4
- **Females-**
  - Clear cell focus 0, 0, 1, 0
  - Focal hepatocytic hyperplasia 1, 0, 1, 0
  - Hepatocytic adenoma 0, 1, 1, 1
  - Hepatocytic carcinoma 0, 0, 0, 0

Pathology Review Examples

Liver Data Evaluation

Antibacterial Agent in Adhesive Formulations

Liver lesions in mice (50/group) as presented by the **petitioner's consultant pathologist for two groups** (0, 150 mg/kg/day)

	incidence / severity
Males-	
Eosinophilic foci	4 (1.2), 3 (2.3)
Basophilic foci	3 (1.0), 3 (2.0)
Hepatocellular adenoma	5 (2.2), 11 (2.9)
Hepatocellular carcinoma	3 (2.3), 2 (1.0)
Total adenoma + carcinoma	8 , 13
Females-	**incidence / severity**
Eosinophilic foci	0 (0), 0 (0)
Basophilic foci	0 (0), 0 (0)
Hepatocellular adenoma	1 (1.0), 1 (2.0)
Hepatocellular carcinoma	0 (0), 0 (0)
Total adenoma + carcinoma	1 , 1

Pathology Review Examples
Liver Data Evaluation
Antibacterial Agent in Adhesive Formulations

Liver lesions in mice (50/group) as presented by the **petitioner's consultant pathologist – all groups** (0, 20, 50, 150 mg/kg/day)

Males-	**incidence / severity**
Eosinophilic foci	4(1.2), 0(0), 1(2.0), 3(2.3)
Basophilic foci	3(1.0), 5(3.4), 2(1.5), 3(2.0)
Hepatocellular adenoma	5(2.2), 8(1.7), 13(2.7), 11(2.9)
Hepatocellular carcinoma	3(2.3), 3(2.0), 1(3.0), 2(1.0)
Total adenoma + carcinoma	8 , 11, 14, 13
Females-	**incidence / severity**
Eosinophilic foci	0(0), 0(0), 1(1.0), 0(0)
Basophilic foci	0(0), 0(0), 1(4.0), 0(0)
Hepatocellular adenoma	1(1.0), 0(0), 1(4.0), 1(2.0)
Hepatocellular carcinoma	0(0), 1(2.0), 0(0), 0(0)
Total adenoma + carcinoma	1 , 1, 1, 1

Pathology Review Examples
Liver Data Evaluation
Antibacterial Agent in Adhesive Formulations

Overall Comments / Conclusions

- Initial: When first seen, results seemed equivocal
  - Variable incidence; male mice / more frequent liver proliferative lesions
  - One gender, One treatment group
- Questions (FDA):
  - Two separate reports submitted
  - Incidence differences not addressed / explained
  - Hyperplasia not defined
- Additional Information Requested:
  - Examine low and mid-dose groups
  - Address the discrepancies
- Results / Comments:
  - No statistical difference; discrepancies based on different criteria
  - Majority tumors at terminal sacrifice;
  - No consistent association of treatment with the severity of the lesions
  - No compelling evidence compound produced liver legions

Pathology Review Examples

Liver Data Evaluation

Olestra

Summary incidence of female rats from the 1 and 2 study with basophilic hepatocellular foci

	1 year /15 rats/group		2 year / 50 rats/group	
Group	**Incidence**	**Severity**	**Incidence**	**Severity**
Study 1				
I Control	4	1.0	35	1.8
II (0.99%)	11	1.0	37	2.1
III (4.76%)	12	1.4	38	2.4
IV (9.09%)	14	1.1	42	2.5
Study 2				
I Control	8	1.0	46	1.3
II (9.09%)	15	1.1	47	3.2

Pathology Review Examples
Liver Data Evaluation
Olestra

FDA Review

- Hepatocellular proliferative lesions – foci, treatment related
- No progression to neoplastic process
- Biological significance - questionable
- CAC
- STP Scientific Symposium on hepatocellular foci – cautioned against classifying chemicals as carcinogenic based on foci only
- Case by Case evaluation by FDA

Pathology Review Examples

t-Butyl Alcohol

- Male Rat kidney tumors / renal cortical
- Association with alpha 2 u microglobulin nephropathy / hyaline droplet
- Characteristic for male rat with linear mineralization in the renal papilla
- Human Relevance?

Conclusion

- FDA science based Agency
- In depth objective evaluation
- All inclusive evaluation – weight of evidence approach
- FDA - Requirements for studies published on the web
- Open effective bilateral communication – goal – protecting public health

Acknowledgement

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Questions?