Peer Review

Of Preclinical Safety Studies

A Regulatory Pathologist’s Perspective
FDA / CFSAN Pathology

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Disclaimer

The following opinions or assertions are those of the speakers and do not necessarily reflect the views or policies of the United States Food and Drug Administration (FDA)
Background

Where is CFSAN FDA located
Food and Drug Administration (FDA)

NCTR – National Center for Toxicological Research
OCC – Office of Chief Counsel
OC – Office of the Commissioner
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 Health
CVM – Center for Veterinary Medicine
CTP – Center for Tobacco Products
CFSAN – Center for Food Safety and Applied Nutrition
CFSAN’s DRAFT Leadership Philosophy Statement

We are dedicated professionals committed to excellence in performing our duties. We are motivated by our desire to protect and promote public health. We value and foster the knowledge and creativity that reside within each of us and believe they are integral to all aspects of our work at all levels of the organization. We work in a collaborative and collegial manner across the organization, relying on everyone’s skills, talents, and abilities. We take pride in doing a great job and seeing the impact on public health.

<table>
<thead>
<tr>
<th>Title</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anonymous CFSAN Employee Suggestions (ACES)</td>
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</tr>
<tr>
<td>CAERS</td>
<td>CFSAN Adverse Events Reporting System (CAERS)</td>
</tr>
<tr>
<td>CARTS</td>
<td>CFSAN Automated Research Tracking System</td>
</tr>
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<td>CFSAN Webcasts</td>
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<tr>
<td>EASE</td>
<td>EASE Production Login</td>
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<tr>
<td>ERIC Service Ticketing</td>
<td>Employee Resource Information Center Service Ticketing</td>
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<tr>
<td>GovTrip Website</td>
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</tbody>
</table>
Background

Who is CFSAN Pathology?
Background

What does CFSAN Pathology Do?
CFSAN Pathology

- Review of pathology data from regulatory submissions & regulatory research studies
- Conduct independent slide reviews
- Participate in PWGs
- Center/Agency expertise for toxicological pathology issues
CFSAN Pathology

First level regulatory reviewer

– Requests CFSAN Pathology to clarify specific pathology issues

CFSAN Pathology supports:

– CFSAN Offices, other FDA Centers and regulatory Agencies
Examples
Compound A

-90 day corn oil gavage
-F344 rats
-10/sex/group
Compound A
In males: Study Pathologist called treatment related

-Marginal increase in severity (2+) of background renal tubular mineralization of the inner and outer medulla of male rats.
-Focal and multifocal (1+) dilation of medullary tubules in mid an high dose of male rats
-Severity 1-2+ = < 1% of renal parenchyma affected
-Concomitant Tubular degeneration (90 -100%) – recorded but not commented on in report
Compound A
In males: Study Pathologist called changes non-adverse because

- **Severity** 1-2+ = < 1% of renal parenchyma affected; no functional impairment
- **No corresponding** clin chem / organ weight changes
- No Mineralization in other tissues
## Compound A
### Kidney Histomorphological Findings

<table>
<thead>
<tr>
<th>Tubular change</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose mg/kg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Dilation 1+</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mineralization 1+</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Mineralization 2+</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Degeneration 1+</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Degeneration 2+</td>
<td>0</td>
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</tr>
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</table>
Compound A

How would Peer Review have been helpful?

• Peer Review to improve data accuracy and robustness
• To communicate data observation more clearly
Compound A
How would Peer Review have been helpful?

Grading score
- Threshold of normal vs. severity thresholds; difference between 0, 1, 2…
- Masked / blinded check of the incidences determined – to ensure changes are truly different from background
Compound A

How would Peer Review have been helpful?

- **Second opinion**: species / stain prevalence of changes observed
- **Reporting**: spatial arrangement of changes within the same or different tubules
- **Improved overall** clarity, robustness and strength of data/text presented
Example B
Compound B
- 13 week GLP dog study
- 52 week GLP dog study
- Same sponsor / PR proposed for both studies in study protocols
- Peer review study report – for 13 week study only
Compound B

If PR is part of the GLP Protocol –

What do you think?
Compound B
If you say you will do in the protocol
– and it is not there:
why is that important
?
Compound B

Because – it...

Casts a shadow of a doubt

That things may not be what they seem
Compound B

- Peer review is currently not required by FDA
- But if it is part of the Protocol – GLP “expectation” applies
- If you say you do it, we will look for it – if it is not there: = Deviation – needs explanation
Example C
Compound C

- CD1 mice 18 month oral carcinogenicity study
- SD rat 2 year oral carcinogenicity study
  • Both studies 660 animals each
# Example Compound C

## Layers of Review

<table>
<thead>
<tr>
<th>Review</th>
<th>Male Mice – Harderian Gland Ad &amp; Ca</th>
<th>Male Rats – Thyroid Follicular Cell Ad &amp;Ca</th>
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</thead>
<tbody>
<tr>
<td>Treatment Group</td>
<td>Control Group</td>
<td>H D Group</td>
</tr>
<tr>
<td>Study Pathologist</td>
<td>1/120 0.8%</td>
<td>6/69 8.7%</td>
</tr>
<tr>
<td>First Agency Review</td>
<td>-</td>
<td>+</td>
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## Example Compound C

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<td></td>
<td>H D Group</td>
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<td>+</td>
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**Sponsor:** Outside

**Expert Consultation**

**Internal Quality Control Examination**

Revealed “some discrepancies regarding the original diagnoses; neoplasia incidences in control animals had been under reported”
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<tr>
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<tr>
<td>Sponsor:</td>
<td>5/120</td>
<td>6/69</td>
</tr>
<tr>
<td>Independent Pathology Laboratory Review</td>
<td>4.2%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Second Agency Review</td>
<td><strong>5/120</strong></td>
<td><strong>7/70</strong></td>
</tr>
<tr>
<td>Agency agreed to consider the revised data</td>
<td><strong>4.2%</strong></td>
<td><strong>10%</strong></td>
</tr>
</tbody>
</table>

**BUT!!!!!**
Agency: “Concerns remain with overall study quality – whether diagnoses from tissue slides of all organs were missed or misinterpreted – potentially affecting the overall study conclusions”
## Compound C

### Layers of Review - continued

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<td><strong>Second Agency Review</strong></td>
<td>Overall quality of entire tissue evaluations questioned</td>
<td></td>
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<tr>
<td><strong>Agency initiates:</strong></td>
<td></td>
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<tr>
<td><strong>Agency</strong></td>
<td></td>
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<td><strong>Contractor</strong></td>
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<tr>
<td><strong>Review of Target Organs</strong></td>
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<table>
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<tr>
<th></th>
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<th>5/69</th>
<th>5/120</th>
<th>7/70</th>
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<tbody>
<tr>
<td></td>
<td>3.3%</td>
<td>7.2%</td>
<td>4.2%</td>
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<td>5/120 4.2%</td>
<td>6/69 8.7%</td>
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<tr>
<td>Peer Review Protocol driven</td>
<td>4/120 3.3%</td>
<td>7/70 10%</td>
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<tr>
<td>independent Review of entire Study by Agency Contractor</td>
<td></td>
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<td><strong>Review of Agency Contractor Peer Review Process by CFSAN/Pathology</strong></td>
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Compound C

Agency driven Peer Review entailed:

Reexamination of

All mouse Harderian glands / All rat Thyroid glands – all dose groups

All previously diagnosed proliferative changes (neoplasia / hyperplasia) all organs / all processed dose groups

Recorded process of how difference of opinion between study and review pathologists was brought to resolution

20% randomly selected Mice/Rat, Control/HD-group slides and diagnoses

َا Any additional proliferative change found in tissue of this step triggered review of that tissue from all animals (both sexes) / all processed dose groups
Compound C

Peer Review revealed: additional proliferative changes not previously diagnosed

Mice: alveolar/bronchiolar adenoma and hyperplasia, adrenal subcapsular hyperplasia, ovarian luteoma

Rats: vaginal granular cell tumor, liver foci, medullar and cortical adrenal hyperplasia, cervical stromal hyperplasia, testicular interstitial cell hyperplasia, vaginal granular cell hyperplasia.
Compound C

What did we do: Regulatory Review of the Peer Review

Provided regulatory pathology perspective to assure non pathologist reviewers that:

- Peer review provided assurance that most proliferative changes were diagnosed and reported
- Degree of diagnostic overlap between study and review pathologist resulted in acceptable data sets to assess the compound’s carcinogenic potential
- Peer Review followed the agreed upon PR Protocol
- Data verification that final report data set is of acceptable quality
Summary
Regulatory Perspective on Peer Review

Submission to the Agency for verification of data quality, accuracy, integrity

✓ We cannot judge Peer Review if it is not documented
✓ If Peer Review is in the protocol – document it
✓ Your Peer Review efforts are to us only as clear as your documentation
Peer Review
as a “Win-Win” activity
Acknowledgements

Thanks to

– You – for your attention
– Organizers for invitation
– Professional colleagues for valuable feedback
??? Any Questions ???