Perspective of a Pathologist on peer review in Indian CRO & Industry

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Confidentiality Disclosure Statement

I, Kalaiselvan, hereby declare that Ideas, comments and opinions described during this presentations are my own and do not represent those of my current work affiliation company Syngene International Limited.

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Outline

• Regulatory frame work and regulations in India
• Toxicology Lab Landscape and GLP laboratories in India
• Pathology peer review Practices in Indian labs
Regulatory framework in India

- Central Ministry
- Regulatory Authority
- Regulatory guidelines/Laws
## Indian regulatory framework for toxicity testing

<table>
<thead>
<tr>
<th>Regulated Product</th>
<th>Act</th>
<th>Regulatory Authority</th>
<th>Regulatory Ministry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs &amp; Pharmaceuticals</td>
<td>Drugs &amp; Cosmetics Act, 1940 - Schedule Y</td>
<td>Central Drugs Standard Control Organization</td>
<td>Ministry of Health &amp; Family Welfare</td>
</tr>
<tr>
<td>Cosmetics</td>
<td></td>
<td></td>
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<tr>
<td>Medical Devices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaccines Biologicals &amp; Biosimilars</td>
<td>Drugs &amp; Cosmetics Act 1940 - Schedule Y</td>
<td>Central Drugs Standard Control Organization, Review committee on Genetic Manipulation, Department of Biotechnology</td>
<td>Ministry of Science and Technology, Ministry of Environment &amp; Forests</td>
</tr>
<tr>
<td></td>
<td>DBT Guidelines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food and Food Products</td>
<td>Food standard &amp; Safety Act, 2006</td>
<td>Food standard and Safety Authority of India</td>
<td>Ministry of Health &amp; Family Welfare</td>
</tr>
<tr>
<td>Genetically Modified Crops</td>
<td>Revised Guidelines for Research in Transgenic Plants, 1998</td>
<td>Department of Biotechnology, Genetic Engineering Appraisal committee</td>
<td>Ministry of Science &amp; Technology, Ministry of Environment &amp; Forests</td>
</tr>
<tr>
<td>Pesticide and Agricultural Chemicals</td>
<td>Central Insecticides Act, 1968</td>
<td>Central Insecticides Boards and Registration Committee</td>
<td>Ministry of Agriculture</td>
</tr>
</tbody>
</table>
New Drug Regulation in India: Non-Clinical Toxicity Testing

DRUGS AND COSMETICS (IIND AMENDMENT) RULES, 2005

MINISTRY OF HEALTH AND FAMILY WELFARE
(Department of Health)
NOTIFICATION
New Delhi, the 20th January, 2005

"SCHEDULE Y
[See rules 122A, 122B, 122D, 122DA, 122DAA and 122E]
REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT AND / OR MANUFACTURE OF NEW DRUGS FOR SALE OR TO UNDERTAKE CLINICAL TRIALS

Appendix III
ANIMAL TOXICOLOGY (NON-CLINICAL TOXICITY STUDIES)
Non-clinical toxicity studies for conducting clinical trials

**Phase I**
- Systemic Toxicity studies (appropriate duration),
- Male fertility study,
- In-vitro genotoxicity tests

**Phase II**
- Summary of all the non-clinical safety data already submitted
- Repeat-dose systemic toxicity studies, In-vivo genotoxicity tests
- Segment II reproductive/developmental toxicity study (if female patients of child bearing age are going to be involved)

**Phase III**
- Summary of all the non-clinical safety data (already submitted)
- Repeat-dose systemic toxicity studies (appropriate duration)
- Segment I (if female patients of child bearing age), Segment III (pregnant or nursing mothers or possible adverse effects on foetal development), Carcinogenicity studies (‘cause for concern’ or when the drug is to be used for more than 6 months)
Outline

• Regulatory frame work and regulations in India

• **Toxicology Lab Landscape and GLP laboratories in India**

• Pathology peer review Practices in Indian labs
Toxicology Labs in India

- CRO, 25
- Pharma, 22
- Academia/ Government, 6

As of Sep 2014.

➤ This is an approximate data
Accredited Test Facilities in India

- **29** Test facilities are GLP certified
- Majority performs Animal toxicity studies (23/29)
- **16** AALAC accredited facilities

Preclinical testing guidelines
- Indian regulatory guidelines
- FDA
- OECD
- ICH
- ISO

http://indiaglp.gov.in/TestFacilities.pdf
http://www.aaalac.org/accreditedorgsdirectorysearch/aaalacprgms.cfm Sep 26, 2014
Veterinary/Toxicologic Pathology In India

- STP-India professional organization of Toxicologic Pathologists
- ~1500* Veterinary Pathologists in India
- STPI membership - 190
- 159 registered members of STPI who currently work in India
- 26% CRO, 30 % Pharma R &D, 28% academia, Overseas 15%
- Majority have Advanced degree in Pathology (Master’s and PhD)
- 24 Indian Pathologists are DABTs (Total 60 DABTs in India)
- Indian Board of Toxicologic Pathology
  - Established in October 2011
  - Conducted 3 certification exams
  - 13 IBTP diplomats as of 2014
  - 80 % Success rate

http://toxpathindia.com/ibtp.html - STPI website
http://www.aotox.org/indiandabt.html - Association of Toxicology
Outline

- Regulatory frame work and regulations in India
- Toxicology Lab Landscape and GLP laboratories in India
- **Pathology peer review Practices in Indian labs**
Pathology Peer Review in India: Survey

• No data available for current practice of pathology peer review in India
• A questionnaire was prepared including 10 questions and sent to 42 Organizations
• 38 organizations responded to the questionnaire
  – 19 CRO
  – 16 Pharma R &D
  – 3 Academia
Survey Results

Question: 1

1. Please describe the nature of your organization:

   - CRO: 50.00% (19)
   - R & D industry: 42.11% (16)
   - Academia: 7.89% (3)

Answered: 38, Skipped: 0

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRO</td>
<td>50.00%</td>
</tr>
<tr>
<td>R &amp; D industry</td>
<td>42.11%</td>
</tr>
<tr>
<td>Academia</td>
<td>7.89%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

Total: 38
Survey Results

Question : 2

What type of animal toxicity studies are performed by your organization?

Answered: 38   Skipped: 0

- GLP studies 7.69% (3)
- Non GLP studies 26.32% (10)
- Both GLP and Non-GLP studies 65.79% (25)

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<tr>
<td>GLP studies</td>
<td>7.69%</td>
</tr>
<tr>
<td>Non GLP studies</td>
<td>26.32%</td>
</tr>
<tr>
<td>Both GLP and Non-GLP studies</td>
<td>65.79%</td>
</tr>
<tr>
<td>Total</td>
<td>100%</td>
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</tbody>
</table>
Survey Results

Question : 3

Does your organization practice pathology peer review process?

Answered: 38  Skipped: 0

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>78.95%</td>
</tr>
<tr>
<td>No</td>
<td>21.05%</td>
</tr>
</tbody>
</table>

Total 38
Survey Results

Question: 4

In your organization, what type of studies you do pathology peer review:

- GLP studies 25.00% (8)
- Non GLP studies 28.13% (9)
- Both GLP and Non GLP studies 46.88% (15)

Answered: 32  Skipped: 6
Survey Results

Question: 5

The need for pathology peer review is based on:

- Sponsor's request: 28.57% (10)
- Default for every study: 11.43% (4)
- Other (please specify): 8.57% (3)
- Case by case basis (only if there is any issue): 51.43% (18)

Table:

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</thead>
<tbody>
<tr>
<td>Default for every study</td>
<td>11.43%</td>
</tr>
<tr>
<td>Sponsor's request</td>
<td>28.57%</td>
</tr>
<tr>
<td>Case by case basis (only if there is any issue)</td>
<td>51.43%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>8.57%</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
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</tbody>
</table>
Survey Results

Question : 6

Mostly, who performs pathology peer review for animal toxicity studies:

Answered: 33  Skipped: 5

- A. Sponsor’s pathologist: 3.03% (1)
- B. Consultant (independent) pathologist: 27.27% (9)
- C. Internal Pathologist (from your organization): 33.33% (11)
- Both A, B & C: 33.33% (11)
- Both A and B: 9.09% (3)

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
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<tbody>
<tr>
<td>A. Sponsor’s pathologist</td>
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<td>C. Internal Pathologist (from your organization)</td>
<td>27.27%</td>
</tr>
<tr>
<td>Both A and B</td>
<td>9.09%</td>
</tr>
<tr>
<td>Both A, B &amp; C</td>
<td>33.33%</td>
</tr>
</tbody>
</table>
Survey Results

Question: 7

After completing the Pathology peer review, how the process is documented in the report

Answered: 33  Skipped: 5

<table>
<thead>
<tr>
<th>Answer Choices</th>
<th>Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process is not documented</td>
<td>12.12%</td>
</tr>
<tr>
<td>By providing a pathology peer review report which is included in the study report</td>
<td>60.61%</td>
</tr>
<tr>
<td>By providing a pathology peer review report which is archived on study files but not included in study report</td>
<td>21.21%</td>
</tr>
<tr>
<td>Either a or b</td>
<td>3.03%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>3.03%</td>
</tr>
</tbody>
</table>

Total: 33
Survey Results

Question : 8

During the process of pathology peer review, what sort of paper work is generated and recorded:

Answered: 33  Skipped: 5

- Individual sheets are included: 30.30% (10)
- Only pathology peer review report/memo is generated and archived: 60.61% (20)
- Other (please specify): 9.09% (3)

<table>
<thead>
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<th>Responses</th>
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</thead>
<tbody>
<tr>
<td>Only pathology peer review report/memo is generated</td>
<td>60.61%</td>
</tr>
<tr>
<td>Individual sheets are included</td>
<td>30.30%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>9.09%</td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
</tr>
</tbody>
</table>
Survey Results

Question : 9

If there is a disagreement between study pathologist and peer review pathologist, how this is resolved:

Answered: 32  Skipped: 8

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>We never had this situation</td>
<td>53.13%</td>
</tr>
<tr>
<td>Independent pathologist (expert neither sponsor your organization) is being asked to review the slides</td>
<td>25.00%</td>
</tr>
<tr>
<td>A panel of expert is being organized (Pathology working group) to review</td>
<td>9.38%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>12.50%</td>
</tr>
</tbody>
</table>

Total 32
Survey Results

Question: 10

Your opinion about the new OECD document on pathology peer review (Document 16)

Answered: 33  Skipped: 5

- Process is clearly explained and is easy to adopt: 81.82% (27)
- Process is complicated and is difficult to adopt: 12.12% (4)
- Other (please specify): 6.06% (2)

<table>
<thead>
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<tbody>
<tr>
<td>Process is clearly explained and is easy to adopt</td>
<td>81.82%</td>
</tr>
<tr>
<td>Process is complicated and is difficult to adopt</td>
<td>12.12%</td>
</tr>
<tr>
<td>Other (please specify)</td>
<td>6.06%</td>
</tr>
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</table>

Total: 33
Survey highlights

• 80% of the labs performing peer review (PR)
• 50% of labs perform PR on a case by case basis
• 12% of labs – PR process is not documented
• 21% of labs - PR report is archived but not included in study report
• 60% of labs – Only PR report is generated and archived, individual sheets are not retained
• 53% of labs – No disagreement during PR
Peer review procedure – Best Practices

• Not a regulatory requirement
• The need for peer review is identified in study plan
• Test Facility should have a SOP describing peer review process
• The peer review procedure is generally as per STP position paper
• 30% of animal from control and high dose – rodent studies
• All the target organs in all the groups
• 10% of animals from carcinogenicity studies
  – Including all neoplastic and hyperplastic findings

Peer review procedure – Best Practices

• Peer review is usually conducted by sponsor/consultant/in-house pathologist

• Location
  – Overseas (sponsor/consultant place)
    • Slides are shipped
    • Discussion through E-Mail / teleconference
      – Document 16 - minutes of teleconferences should be included and archived in study file
  – Test site
    • Peer review pathologist visit the test site
Peer review procedure – Best Practices

• Procedure
  – Test site procedure
  – Occasionally sponsor’s procedure
  – Starts after primary pathology evaluation
  – Draft pathology report and study details shared with peer reviewer
  – The study pathologist and peer review pathologist observations are compared and recorded
  – Difference of opinion is resolved and mutually accepted diagnosis recorded
  – The peer review pathologist issues Peer review statement
  – Formation of PATHOLOGY WORKING GROUP – rare

• Outcome
  – Beneficial to sponsor – pathology data is technically quality checked
  – Beneficial to study pathologist – Learning opportunity
OECD Document 16 - Challenges

- Any differences of interpretation that result in a significant change of the study pathologist’s original interpretation should be discussed in the final report.
- Minutes of teleconferences to be retained in study file.
- Reporting of the peer review should be sufficiently detailed to allow reconstruction of the process and of the opinions expressed.
Acknowledgements

• Survey Participants
• Dr. Bhanu Singh, BVSc, MS, DACVP, DABT, Fellow IATP Scientific Director, Janssen R&D, USA
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