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 frame work in India

- Central Ministry
- Regulatory Authority
- Regulatory guidelines/Laws

Indian regulatory framework for toxicity testing

Regulated Product	Act	Regulatory Authority	Regulatory Ministry
Drugs & Pharmaceuticals	Drugs & Cosmetics Act, 1940 - Schedule Y	Central Drugs Standard Control Organization	Ministry of Health & Family Welfare
Cosmetics			
Medical Devices			
Vaccines Biologicals & Biosimilars	Drugs & Cosmetics Act 1940 - Schedule Y DBT Guidelines	Central Drugs Standard Control Organization, Review committee on Genetic Manipulation, Department of Biotechnology	Ministry of Science and Technology Ministry of Environment & Forests
Food and Food Products	Food standard & Safety Act, 2006	Food standard and Safety Authority of India	Ministry of Health & Family Welfare
Genetically Modified Crops	Revised Guidelines for Research in Transgenic Plants, 1998	Department of Biotechnology, Genetic Engineering Appraisal committee	Ministry of Science & Technology, Ministry of Environment & Forests
Pesticide and Agricultural Chemicals	Central Insecticides Act, 1968	Central Insecticides Boards and Registration Committee	Ministry of Agriculture

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

Apendix 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)

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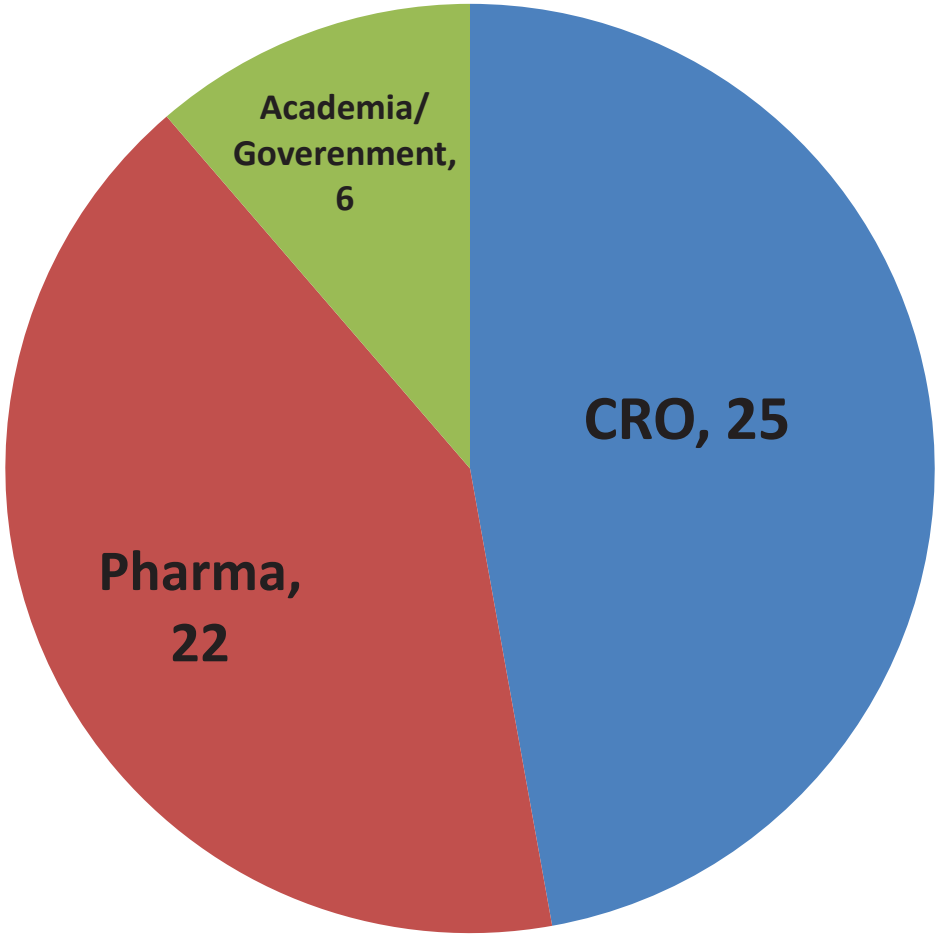
Toxicology Labs in India



As of Sep 2014.

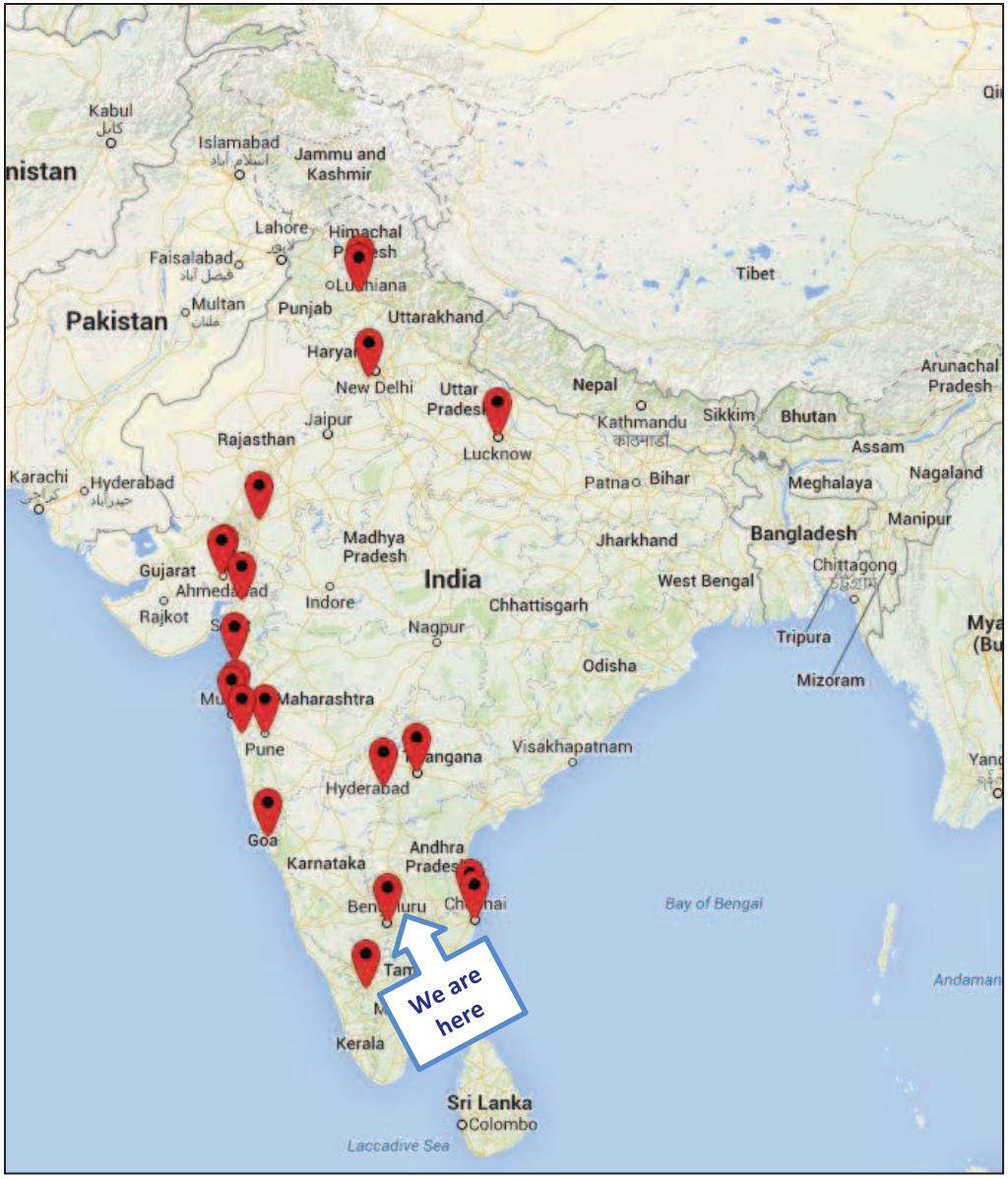
- This is an approximate data

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

•* Schultze AE, Reddy VR, Donnelly KB, Berridge BR. Toxicologic pathology in a multicultural world--India. Toxicol Pathol. 2011 Oct;39(6):1003-9

•http://toxpathindia.com/ibtp.html - STPI website

•http://www.aotox.org/indiandabt.html - Association of Toxicology

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- **Pathology peer review Practices in Indian labs**

Pathology Peer Review in India: Survey

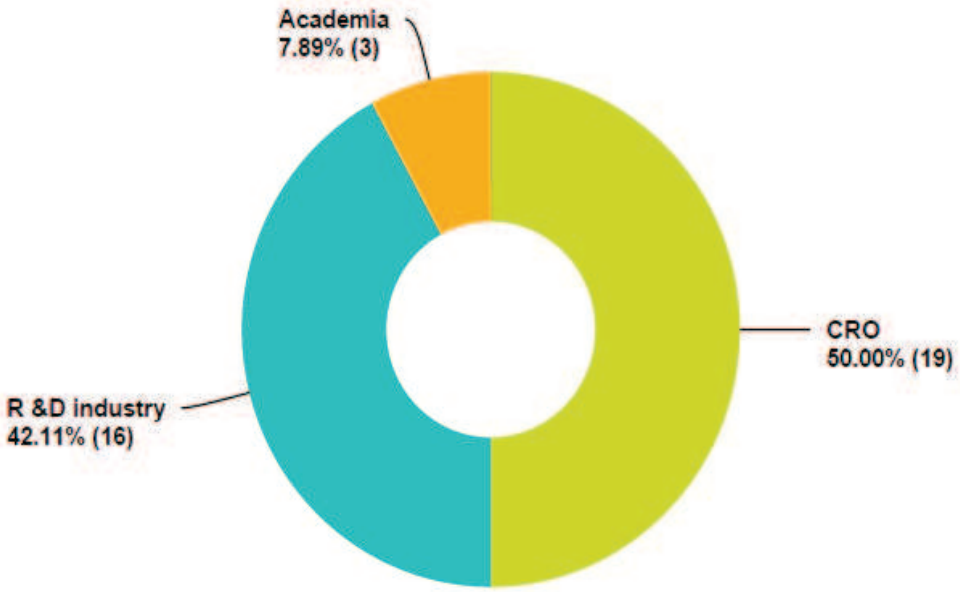
- No data available for current practice of pathology peer review in India
- A questionnaire was prepared including 10 questions and sent to 42 Organizations
- 38 organizations responded to the questionnaire
  - 19 CRO
  - 16 Pharma R &D
  - 3 Academia

Survey Results

Question : 1

1. Please describe the nature of your organization:

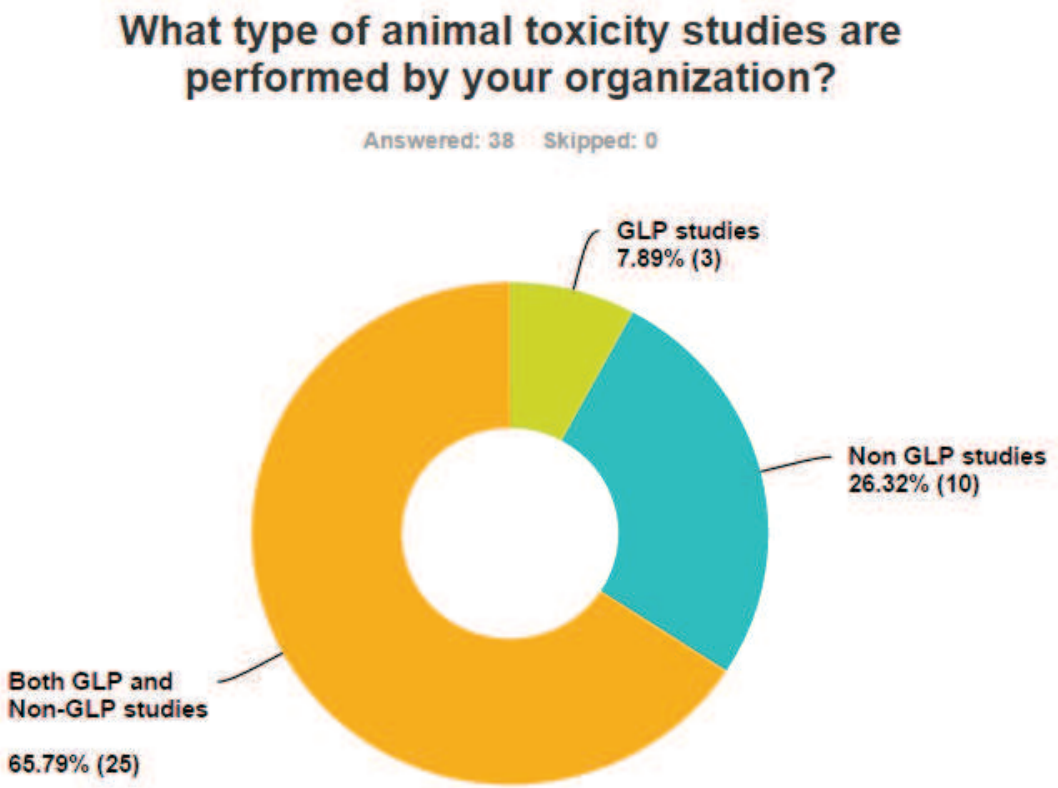
Answered: 38 Skipped: 0



Answer Choices		Responses	
CRO		50.00%	19
R &D industry		42.11%	16
Academia		7.89%	3
Other (please specify)	Responses	0.00%	0
Total			38

Survey Results

Question : 2



Answer Choices	Responses	
GLP studies	7.89%	3
Non GLP studies	26.32%	10
Both GLP and Non-GLP studies	65.79%	25
Total		38

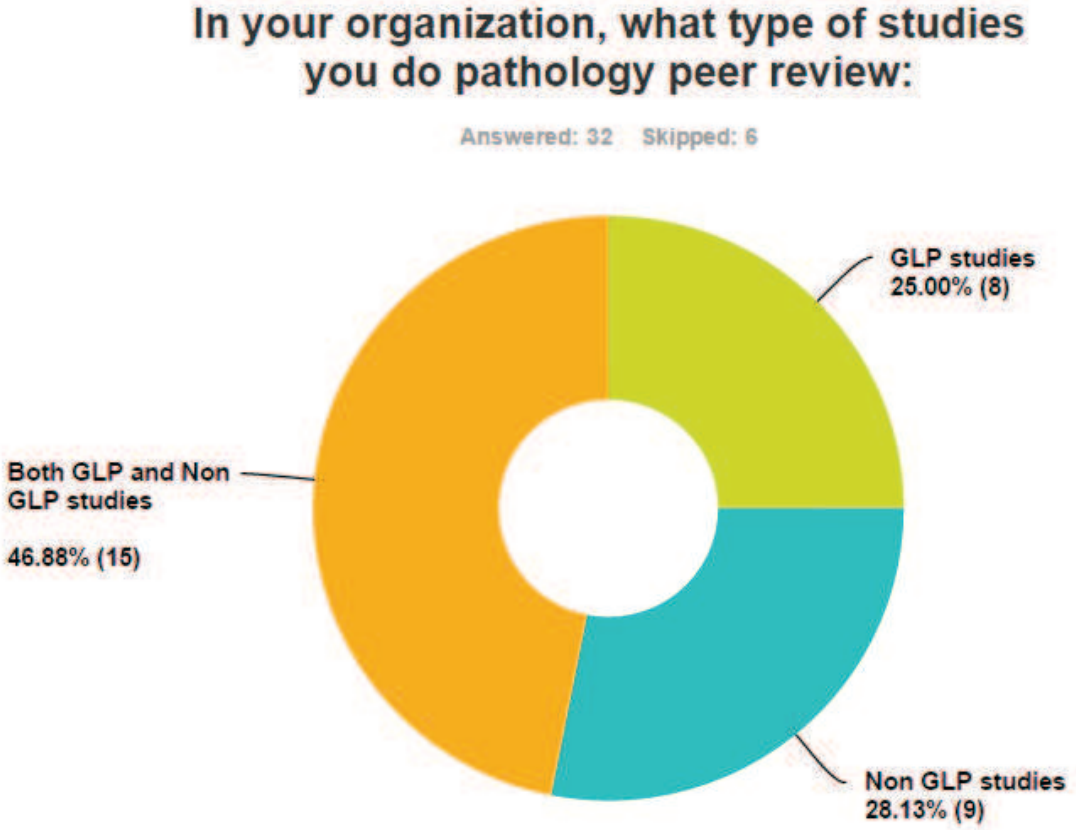
Survey Results

Question : 3

Answer Choices	Responses	
Yes	78.95%	30
No	21.05%	8
Total		38

Survey Results

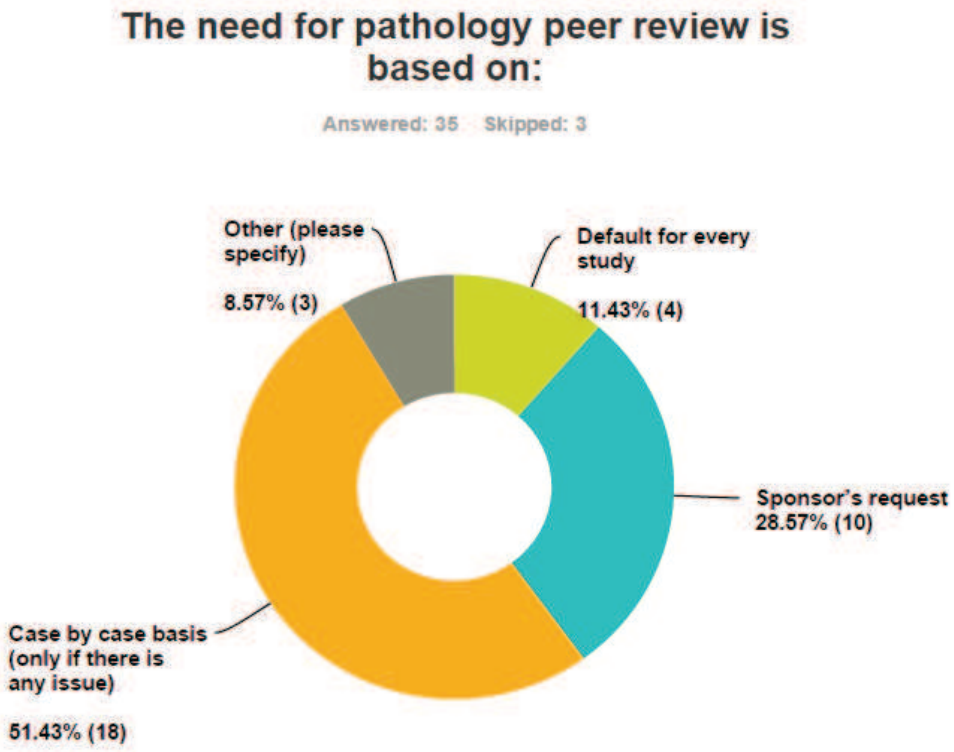
Question : 4



Answer Choices	Responses	
GLP studies	25.00%	8
Non GLP studies	28.13%	9
Both GLP and Non GLP studies	46.88%	15
Total		32

Survey Results

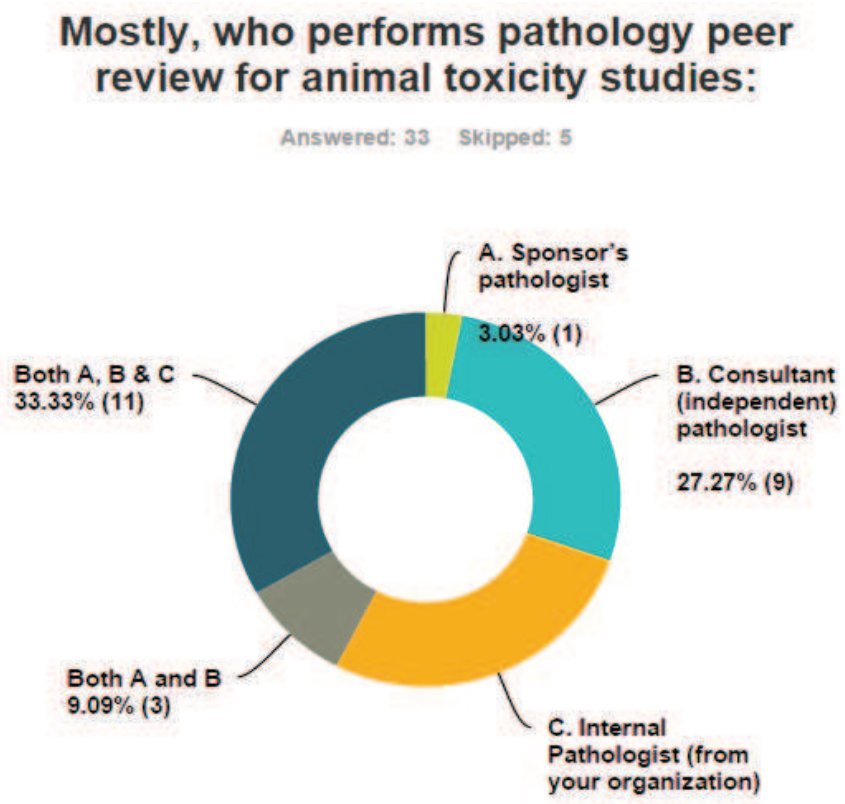
Question : 5



Answer Choices		Responses	
Default for every study		11.43%	4
Sponsor's request		28.57%	10
Case by case basis (only if there is any issue)		51.43%	18
Other (please specify)	Responses	8.57%	3
Total			35

Survey Results

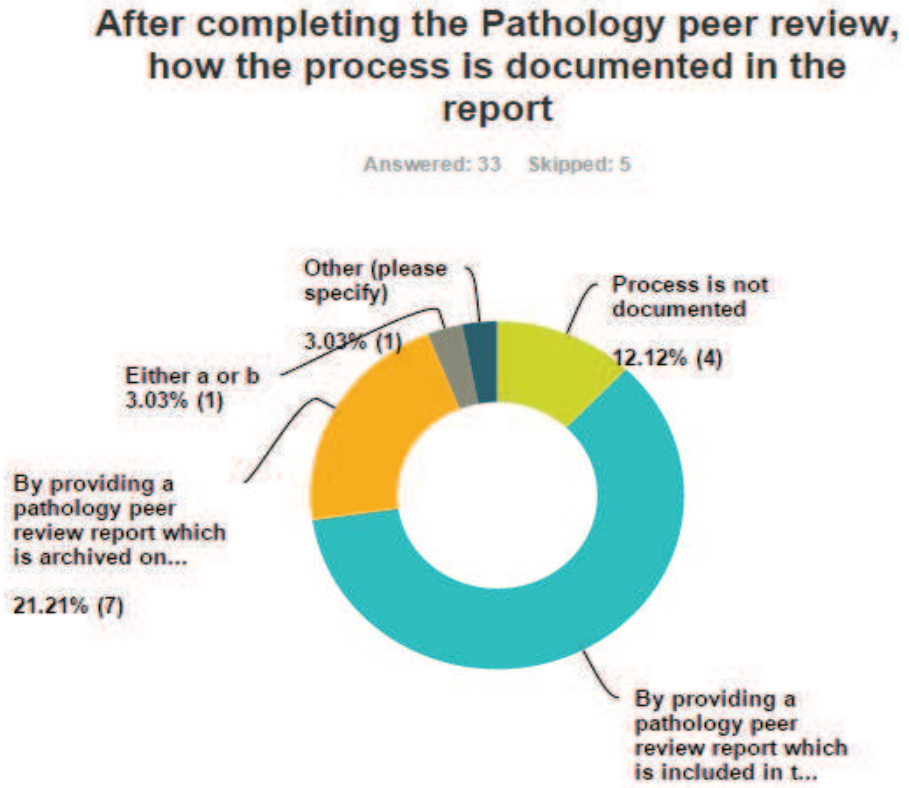
Question : 6



Answer Choices	Responses	
A. Sponsor's pathologist	3.03%	1
B. Consultant (independent) pathologist	27.27%	9
C. Internal Pathologist (from your organization)	27.27%	9
Both A and B	9.09%	3
Both A, B & C	33.33%	11
Total		33

Survey Results

Question : 7



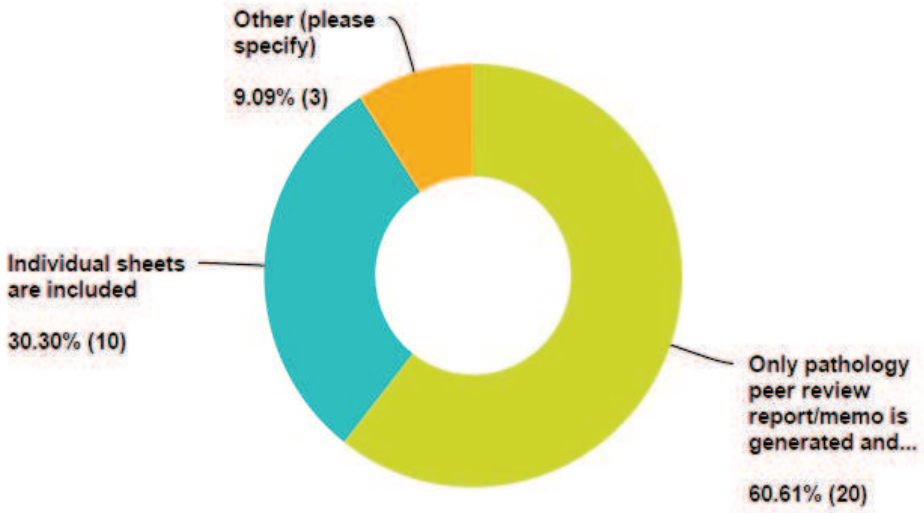
Answer Choices	Responses	
Process is not documented	12.12%	4
By providing a pathology peer review report which is included in the study report	60.61%	20
By providing a pathology peer review report which is archived on study files but not included in study report	21.21%	7
Either a or b	3.03%	1
Other (please specify) Responses	3.03%	1
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



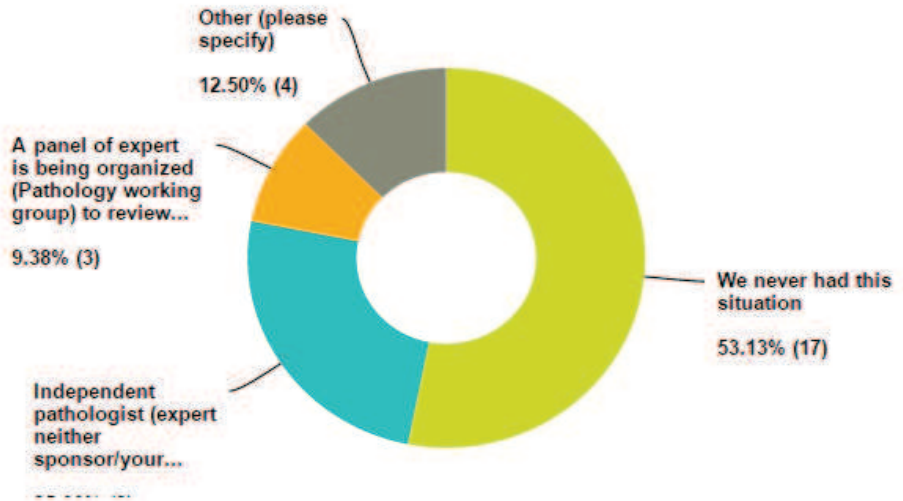
Answer Choices		Responses	
Only pathology peer review report/memo is generated and archived		60.61%	20
Individual sheets are included		30.30%	10
Other (please specify)	Responses	9.09%	3
Total			33

Survey Results

Question : 9

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

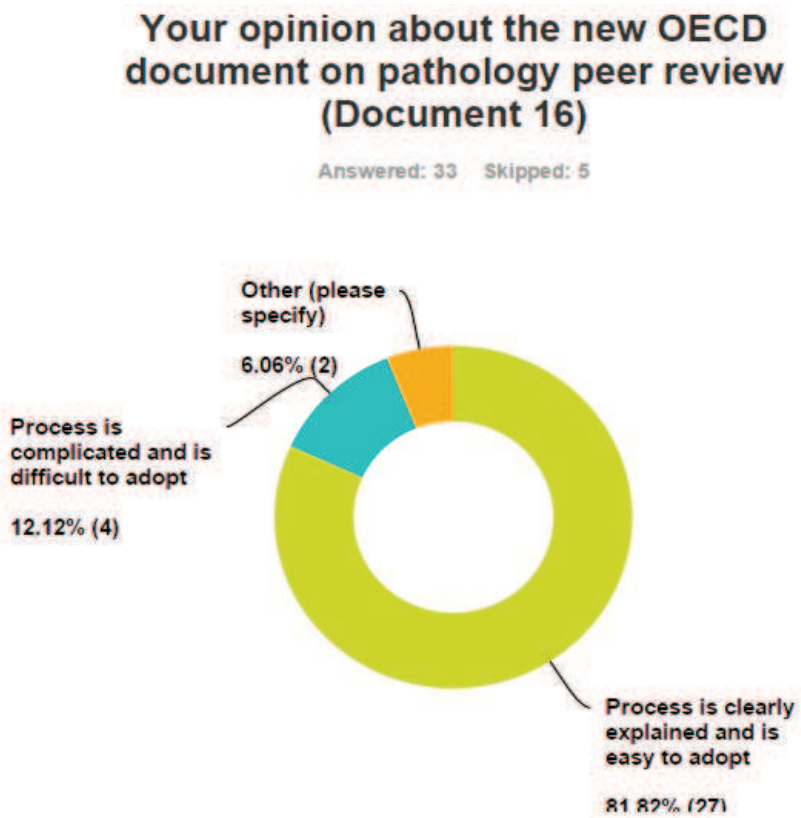
Answered: 32 Skipped: 6



Answer Choices	Responses	
We never had this situation	53.13%	17
Independent pathologist (expert neither sponsor/your organization) is being asked to review the slides	25.00%	8
A panel of expert is being organized (Pathology working group) to review the slides	9.38%	3
Other (please specify) Responses	12.50%	4
Total		32

Survey Results

Question : 10



Answer Choices		Responses	
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)	Responses	6.06%	2
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

Morton D, Sellers RS, Barale-Thomas E, Bolon B, George C, Hardisty JF, Irizarry A, McKay JS, Odin M, Teranishi M. **Recommendations for pathology peer review.** Toxicol Pathol. 2010 Dec;38(7):1118-27

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.

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Number 16

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