Regulatory views on Pathology results

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Regulatory Views on Pathology results

TOXICOLOGICAL PATHOLOGISTS DO IT WITH SLICES

But they do not have the monopoly

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Fruit shops

Bakers

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TOXICOLOGICAL PATHOLOGY in the development of human pharmaceuticals

Pathology as important issue on our regulatory table

- General Toxicity
- Reproductive toxicity
- Immunotoxicity
- Carcinogenicity

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General toxicity, early phase

Repeated dose toxicity

• 1 month study in rodents and nonrodents
  – Fertility measures, histopathology of testis and uterus
  – Immunotoxicity, first assessment of histopathology of lymphoid organs: spleen, thymus, lymph nodes
  – Signals of organ toxicity (liver/kidney etc).

→ Important for First-in Human trials
General toxicity, later phase

Repeated dose toxicity
- 6 months study in rodents
- 9 months study in nonrodents (dogs/minipigs/monkeys)
  - Histopathology of all organs

→ Important for Phase 3 and Marketing Authorisation

→ Also for first estimate of carcinogenic potential (see later)
Interpretation

• What are species-specific effects?
  - E.g. vacuolation
  - Phospholipidosis
  - Other phenomena

What is the relevance for humans?

• Biomarkers: easy to have, if validated. Interpretation is dependent on histopathological explanation.

• Hyperplasia vs. Hypertrophy
  - Important for prediction of carcinogenicity outcome.
  - (to be discussed later)

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Reproductive Toxicity

• Classical approach
  – Embryofetal Developmental toxicity studies in two species
  – Adverse effects established by macroscopy, i.e. malformations and tissue changes
  – More in depth screening with histopathological methods

• Recent developments
  – Introduction of in vitro approaches
  – Reduction of in vivo mammalian approaches
    • e.g. two-species debate, rat vs. rabbit, which one is the most sensitive species
Introduction of a two-step tiered testing Approach

- All new investigational drugs should be evaluated for the potential to produce immunotoxicity.

- Methods include
  1. standard toxicity studies: Haematology, lymphoid organ weights and histology, bone marrow cellularity
  2. additional immunotoxicity studies: Impairment of cell function at the effector or regulatory level (including host resistance models)

The need for additional immunotoxicity studies will be determined by a weight of evidence review of causes for concern.
Weight-of-Evidence Review

- A decision making approach for immunotoxicity testing
- Six factors to consider as areas of concern
- If a cause for concern is present
  - Sponsors should conduct studies of drug effect on immune function or
  - Sponsors should provide justification for not performing the evaluations
- A finding of sufficient magnitude in a single area should trigger Additional Immunotoxicity Studies
- Findings from more than one factors (not sufficient on its own) could trigger Additional Immunotoxicity Studies

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Factors To Be Considered

- Standard Toxicity Studies
- Pharmacological properties
- Intended patient population
- Structural similarity
- Disposition of the drug
- Clinical information

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Immunotoxicity S8

- Hematological changes (leukocytosis, lymphopenia)
- Alterations in immune system organ weights and histology
- Changes in serum globulins might be an indication for changes in immunoglobulins

Other evidence
- Incidence of infections
- Evidence of carcinogenicity in absence of other plausible causes
Recommended Considerations in Reviewing Standard Toxicity Study Data

Regulatory Views on Pathology results

Immunotoxicity S8

- Standard and biological significance
- Severity of effects
- Dose/exposure relationship
- Safety factor above the expected clinical dose
- Number of species and endpoints affected
- Secondary effects (e.g. Stress)
- Cellular targets and/or mechanisms
- Immunotoxic dose vs other toxicities
- Reversibility of effects

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Evolving concepts in carcinogenicity testing

In the past
- Life long testing
- In Two Species
- Maximum Tolerable Dose
- Emphasis on Statistics

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What is the impact of a slice?

- To take a decision on the carcinogenic potential

Tumor?

Yes

Adenoma or carcinoma

Adenoma: weak(er) signal

Progress?

Carcinoma: strong signal
Important Issues in carcinogenicity testing

- Benign-malignant
- Time dependent progress
- Single or two species
- Same or different site

All decisions based on slices

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What is the relevance of all these slices

- 50% of all chronically used human pharmaceuticals induce tumors in rodents
- Only 20 human pharmaceuticals have been identified by epidemiology, although a lot of epidemiological studies have been carried out e.g. NSAID’s, benzodiazepines, phenobarbital
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Relevant factors

- From the viewpoint of compound testing
  
  MULTI STAGE MODEL

  - DNA-damage (direct or indirect)

  Initiation

  - Proliferative activity to fixate the genetic damage

  Promotion

  Human pharmaceuticals are almost exclusively nongenotoxic.

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What is cancer?

(Hanahan, Weinberg, Hallmarks of cancer: the next generation. Cell. 2011; 144;646-674)
### Mechanistic Parameterisation

<table>
<thead>
<tr>
<th>Component</th>
<th>Acquired Capability</th>
<th>Example of Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Flag" /></td>
<td>Self-sufficiency in growth signals</td>
<td>Activate H-Ras oncogene</td>
</tr>
<tr>
<td><img src="image" alt="Plant" /></td>
<td>Insensitivity to anti-growth signals</td>
<td>Lose retinoblastoma suppressor</td>
</tr>
<tr>
<td><img src="image" alt="Cross" /></td>
<td>Evading apoptosis</td>
<td>Produce IGF survival factors</td>
</tr>
<tr>
<td><img src="image" alt="Infinity" /></td>
<td>Limitless replicative potential</td>
<td>Turn on telomerase</td>
</tr>
<tr>
<td><img src="image" alt="Heart" /></td>
<td>Sustained angiogenesis</td>
<td>Produce VEGF inducer</td>
</tr>
<tr>
<td><img src="image" alt="Magnifying Glass" /></td>
<td>Tissue invasion &amp; metastasis</td>
<td>Inactivate E-cadherin</td>
</tr>
</tbody>
</table>

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MECHANISTIC PARAMETERISATION

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Nongenotoxic Carcinogens

From Hanahan and Weinberg, 2011

Cancer-Associated Fibroblast (CAF)
Endothelial Cell (EC)
Pericyte (PC)

Cancer Stem Cell (CSC)
Immune Inflammatory Cells (ICs)

Invasive Cancer Cell

Local & Bone marrow-derived Stromal Stem & Progenitor Cells

Core of Primary Tumor microenvironment
Invasive Tumor microenvironment
Metastatic Tumor microenvironment
Progress in dissecting signalling pathways has begun to lay out a circuitry that will likely mimic electronic integrated circuits in complexity and finesse, where transistors are replaced by proteins (e.g., kinases and phosphatases) and the electrons by phosphates and lipids, among others. As for the genetic reprogramming of this integrated circuit in cancer cells, some of the genes known to be functionally altered are highlighted in red.
Evolution of Carcinogenicity testing

Life-long testing

Short term testing with enhanced predictability
- Transgenic mice
- Mechanistics testing
- Weight-of-evidence approach
- Toxicogenomics/proteomics?

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Should pathologists change jobs?

- Pathologists are still needed to conduct more relevant studies

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The actual situation

- Potential revision of ICH approach of S1
  a. Need for studies for compounds used 3-6 months – 6 months data
  b. Still two rodent species are needed, rats and mice
- NEGCARC approach
  - Use of knowledge of 6-months data
- ICH S1 Regulatory Notice Document
- Evaluation of CAD’s
- Recommendations

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Quality assurance in pathology

- Peer review
  - important for at least 10% of animals, and all target organs
- Blinded slide reading
  - not recommended for routine examination
  - can be helpful with equivocal findings
- Evaluation process
  - only one pathologist per study
  - if not, extensive peer review is needed to assure consistency
- Qualification of involved scientists
  - considered crucial, Board Certification?
  - academic degree with postgraduate training
NEGCARC approach

- N egative histopathology after 6 months
- E (absence of) endocrine effects
- G (absence of) genotoxicity
- C
- A
- R
- C

When all criteria would be fulfilled the outcome of the 2-yr rat study will be negative.
Sistare et al, 2011
NEGCAp approach

Are histopathologic risk factors for neoplasia* seen anywhere in the whole animal in chronic rat toxicology studies predictive of tumor outcome at any site in 2-year rat bioassays?

*Histo positive (His+): all microscopic histologic terms indicative of a potential neoplastic outcome:
1) Hyperplasia – i.e., “hyperplasia, basophilia, multinucleated cells, ...”
2) Cellular hypertrophy - i.e., “hypertrophy, cellular enlargement, cytomegaly, ...”
3) Foci of cellular alteration – i.e., “eosinophilic foci, basophilic foci, dysplasia, tumor, ...”

Histo negative (His-): Absence of context appropriate histopathologic risk factors of neoplasia.

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Data collected:

- **Chronic Rat Study Histopathology Data**
  - Clear treatment-related microscopic changes seen in designated risk factors of neoplasia

- **Genotoxicity Study Data**
  - Clear positive in one or more of the standard genetox test battery

- **Evidence of Hormonal Perturbation:**
  - Microscopic &/or macroscopic changes in multiple endocrine organs in the chronic rat study, &/or hormone measurements in any rat study, &/or knowledge of intended endocrine target

- **Mouse Carco Study Data:**
  - Significant tumor finding in any tissue of 2-yr or 6-m transgenic mouse study

- **Marketing Information:**
  - Marketed; Still In Development; Discontinued for other Reasons; or "Not marketed because of tumor findings."

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PhRMA hypothesis...

That a rat chronic tox study will identify an effect that would define the need for completing a 2-yr rat assay, i.e.,

(+) His in any tissue, genetox positive, or clear evidence of hormonal perturbation run a 2-year bioassay

(-) His in all tissues, no genetox, and no evidence of hormonal perturbation conclude no carcinogenic concern & no need to perform the 2-year rat study

Rationale:

1) tumorigenic processes are often dependent on multi-organ participation (e.g., liver/thyroid; pituitary/mammary)
2) tumorigenic compounds of higher concern are multi-site/species/-sex; so sensitivity enhanced using “any organ” signal
3) operationally, whether FP or TP site makes no difference - any signal seen will trigger rat carco study

Do the data support this hypothesis?

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Negative prediction

Rat chronic toxicology studies are good predictors of negative outcome in 2 yr rat carcinogenicity studies:

Sistare et al 2011

a) Results derived from 182 compounds across 242 rat chronic tox studies and 182 2-yr rat carcinogenicity studies conducted by 13 pharma companies over 25+ years.

b) Predictivity on an organ by organ basis is poor, but overall negative predictivity is very good on a whole animal basis. NO chronic tox preneoplasia + NO genetox + NO hormonal perturbation signals = NO value added from 2 yr rat carco study.

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Conclusions on negative prediction

The data collected indicate that a site based tumor prediction is not effective, but may also be irrelevant to the utility of the approach.

A paradigm of integrating:
• 1) chronic rat study preneoplasia histo on a whole animal basis,
• 2) genetox results, and
• 3) evidence for chronic rat hormonal perturbation,

demonstrates approximately 80% sensitivity and negative predictivity for RAT carcinogenicity outcome.

Refining to these criteria as triggers for 2-yr Rat Carco Testing would yield a significant reduction of 40% in Rat 2-yr Carco Study conduct and a significant reduction in development time.

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What are neoplastic phenomena?
• Hyperplasia
• Foci
Or
• Hypertrophy

Criteria of Sistare et al 2011:
*Histo positive (His+): all microscopic histologic terms indicative of a potential neoplastic outcome:
1) Hyperplasia – i.e., “hyperplasia, basophilia, multinucleated cells, ...”
2) Cellular hypertrophy - i.e., “hypertrophy, cellular enlargement, cytomegaly, ...”
3) Foci of cellular alteration – i.e., “eosinophilic foci, basophilic foci, dysplasia, tumor, ...”
## Carcinogenicity Dataset in S1 2011

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
<th>PhRMA</th>
<th>FDA</th>
<th>JPMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>74</td>
<td>45</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>48</td>
<td>32</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Respiratory</td>
<td>23</td>
<td>18</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Metabolic</td>
<td>28</td>
<td>18</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Hormonal</td>
<td>20</td>
<td>13</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>15</td>
<td>14</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Antiviral</td>
<td>24</td>
<td>17</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>Antimicrobiological</td>
<td>16</td>
<td>15</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Remaining</td>
<td>47</td>
<td>15</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>295</td>
<td>187</td>
<td>44</td>
<td>64</td>
</tr>
</tbody>
</table>
NEG CARC Proposal PhRMA
- 21 False Negatives,
  - i.e. negative after 6 and tumors after 24 months

What is the impact of these False Negatives (FN’s)?

PhRMA Individual discussion of the cases

EU Integrated approach of all cases.
FN’s are exceptions on the rule
  » The rule is not a real concern or a well-known risk

Therefore: FN’s does not change eventually the outcome

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New text in Addendum S6 (2011)

Carcinogenicity (1)

This strategy could be based on a weight of evidence approach, including a review of relevant data from a variety of sources. The data sources can include published data

- information on class effects,
- detailed information on target biology and mechanism of action, \textit{in vitro} data,
- data from chronic toxicity studies and clinical data.

In some cases the available information can be sufficient to address carcinogenic potential and inform clinical risk without additional nonclinical studies.
Carcinogenicity (2)

- The mechanism of action of some biopharmaceuticals might raise concern regarding potential for carcinogenicity (e.g., immunosuppressives and growth factors). If the weight of evidence (see previous slide) supports the concern regarding carcinogenic potential, rodent bioassays are not warranted.

- In this case potential hazard can be best addressed by product labeling and risk management practices. However, when the weight of evidence is unclear, the sponsor can propose additional studies that could mitigate the mechanism-based concern.
## Positive classes

### Classes with high percentage of rat carcinogens related to pharmacology

<table>
<thead>
<tr>
<th>Class</th>
<th>total number of compounds</th>
<th>Compounds With Tumors</th>
<th>True positives</th>
<th>False negatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DA&lt;sub&gt;2&lt;/sub&gt;-antagonists</td>
<td>13</td>
<td>9 (71%)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>3 5HT&lt;sub&gt;2&lt;/sub&gt;-antagonists</td>
<td>3</td>
<td>3 (100%)</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>30 Adrenergic β&lt;sub&gt;2&lt;/sub&gt;-agonists</td>
<td>5</td>
<td>3 (60%)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>33 PPAR-γ agonists</td>
<td>8</td>
<td>7 (88%)</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>34 HMG-CoReductase inhibitors</td>
<td>5</td>
<td>4 (80%)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>36 Estrogen Modulators</td>
<td>4</td>
<td>3 (75%)</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>38 Aromatase inhibitors</td>
<td>5</td>
<td>3 (60%)</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>-48 Proton pump inhibitors</td>
<td>4</td>
<td>3 (75%)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>49 H2 antagonists</td>
<td>4</td>
<td>3 (75%)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>51 Vit D analogues</td>
<td>4</td>
<td>4 (100%)</td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>

- **True positives**: preneoplastic effects at 6 months
- **False negatives**: no preneoplastic effects at 6 months

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## Negative classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Nr.</th>
<th>With Tumors</th>
<th>No Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 5HT1b/d-agonists (triptanes)</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>5 5HT3-antagonists</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>6 SSRIs</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>8 NMDA-antagonists</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>9 DA/NE-reuptake inhibitors</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>12 GABA-A-agonists</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>15 Ach-esterase-inhibitors</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>17 ACE inhibitors</td>
<td>6</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>18 AII antagonists</td>
<td>6</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>19 Phosphodiesterase 5 inhibitors</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>20 Adrenergic $\alpha_2$-agonists</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>22 Beta blockers</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>23 Vasopressin antagonists</td>
<td>2</td>
<td>-</td>
<td>2</td>
</tr>
<tr>
<td>39 Anti-inflammatory</td>
<td>11</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>44 Anthelmintics</td>
<td>3</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>50 Anticholinergics</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
</tbody>
</table>
Inconclusive classes

<table>
<thead>
<tr>
<th>Class</th>
<th>Nr.</th>
<th>With Tumors</th>
<th>No Tumors</th>
<th>True positive</th>
<th>False negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>- α2δ-agonists</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ DA2-agonists</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musc. M1 agonists</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- μ-opioid agonists</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>α2a-antagonists</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenergic α1 antagonists</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukotriene Receptor antagonists</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- H1 antihistamines</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gliptins</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Phosphodiesterase4 inhibitors</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Testosterone inhibitors</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>GnRH-antagonists</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>+ Immunosuppressants/modulators</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Biphosphonates</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
New Hypothesis

When outcome is predictable, studies are not needed

- **Positive prediction**: Mainly on the basis of pharmacology. Positive classes support positive prediction

- **Negative prediction**: mainly based on absence of histopathology. Negative classes can support a ‘false negative’ results.

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Compounds can be categorized in 3 categories:

1. Compounds with high certainty being human carcinogens
   • no carcinogenicity studies needed. Only labelling
2. Compounds with uncertainty being human carcinogens
   • Carcinogenicity studies might have added value and should be conducted.
3. Compounds with high certainty being human noncarcinogens
   • With negative histopath at 6 months, no signal from pharm or genetox: ---> no tumors to be expected
   • With positive pharmacology signals, and confirming histopath → tumors to be expected, but no relevance to human situation

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Virtual waiver request
Companies are requested to write a Carcinogenicity Assessment Document summarizing:

- «Target and pathway –related mechanistic /pharmacologic and understood pharmacologic characteristics can contribute to the prediction of outcomes of carcinogens»
- Genotoxicity
- Repeated dose toxicity in rats (6 months)
- And all other relevant data

Leading to a statement in which category
- about the predictivity of the carcinogenicity
- the need of a carcinogenicity study
- Or the request of waiver.
Evaluation after 17 CAD’s

Most important categories in this Regulatory experiment:
• 3A and 3B: Request for virtual waivers

However:
• Sponsors proposed 12 in Category 3, while Regulators maintained only 4 in Category 3, the remaining putting in Category 2.
  • Equivocal nature of short-term findings
  • Theoretical risk from the drug’s MoA, neglected by sponsor or considered unimportant.
  • In ‘real live’ companies would have been requested to do additional mechanistic studies

Solution:
• Wait for the outcome, and see who was “right”. 😃.
• Enhance the quality of the predictions in the CAD. See Recommendations

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Recommendations (1)

Companies submitting CAD’s are encouraged to:

- Better characterise/present/discuss primary and off-target pharmacology
  - Role of gene-expression data?
  - Additional MoA studies to be conducted for secondary findings?
- Refine use of data from similar compounds in the Weight-of Evidence discussion
  - What is the number of compounds needed to define a class-effect?
  - What about compounds without mammalian (host) pharmacological targets? (e.g. antivirals, antimycotics)
- Improve literature and referencing.
  - Publicly available cases should not be missed.
Recommendations (2)

Companies submitting CAD’s are encouraged to:

– Involve non-rodent data to discuss relevance for humans, and if applicable provide more data on non-rodent studies.

– This might be especially important for hormonal signals, sometimes obtained in reprotox studies, which seem to be neglected.

– Increase level of information on metabolism comparison between humans and animal species, and if applicable metabolite characterisation studies.
MY DREAM

Any time

NO LIFE TIME
Carcinogenicity studies

send your questions to: questions.ifstp.webinar@gmail.com