Evaluation of Potential Carcinogenicity

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Lecture Outline

- History of carcinogenicity evaluation
- Objective of carcinogenicity evaluation
- Requirement for carcinogenicity studies
- Planning for carcinogenicity study
- Study design (2-year study)
- Transgenic mouse study
- Review of study plan
- Study oversight
- Histopathology
- Statistics
- Interpretation of “positive” results for assessing human relevance
- Regulatory implications of “positive” study result
Chimney Sweeps
First Description of Chemical Carcinogenesis
Scrotal cancer in chimney sweepers in 1775 in England
History of Evaluation of Carcinogenicity

• First demonstration of chemical carcinogenesis in animals
  – Yamagiwa and Ichikawa 1918
  – Rabbit skin tumors related to coal tar administration

• “Standard Chronic Bioassay” for carcinogenicity
  – Started in 1960s
  – Enhanced by National Cancer Institute Program

• National Toxicology Program (NTP)
  – Founded in 1978
  – Significant impact on testing approaches

• ICH Guideline for carcinogenicity testing
  – 1990s
Carcinogenicity Testing
Historical Perspective

- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
- Future

Carcinogenicity Study
Carcinogenicity Observations

Standardized Carcinogenicity Testing

Carcinogenicity Evaluation Experiments

- Sort term assays
- Application of molecular basis of Carcinogenicity
- “Humanized” rodents
Possible Objective of Carcinogenicity Testing

1. Screening chemicals to identify carcinogenicity
2. Characterizing a dose response curve in observable range
3. Characterizing dose response curve to facilitate low dose extrapolation
4. Defining a threshold or benchmark dose departure point
5. Providing data on health effects at human exposure levels
6. Providing data to determine mode of action

Objective of Carcinogenicity Testing

• “The objectives of carcinogenicity studies are to identify a tumorigenic potential in animals and to assess the relevant risk in humans”

ICH S1A
Requirement for Carcinogenicity Studies
Requirement for Carcinogenicity Studies

Requirement for study set by regulatory agencies

• Pharmaceuticals (Standardized by ICH)
  – Requirements essentially the same in US, Europe and Japan
  – Minor differences based on local preferences and on differences in interpretation of ICH guidelines

• Chemicals
  – Greater variation in requirements compared to pharmaceuticals
Requirement for Carcinogenicity Studies

• Historically, two rodent species required with dosing for 18 months to 2 years
• Subsequently 2-year rat and mouse studies became the norm
• Currently for pharmaceuticals, “...one long term rodent carcinogenicity study, plus one other study ...that supplements the long term carcinogenicity study” (ICH S1B)
Requirement for Carcinogenicity Studies

Approaches to supplement a single long term carcinogenicity study

• Initiation-promotion in rodents
• Models of carcinogenesis
  – Transgenic rodents (Specific to be presented later in lecture)
  – Neonatal rodents
• Long term carcinogenicity study in a second rodent species is still acceptable

ICH51B
Requirement for Carcinogenicity Studies
Pharmaceuticals
Factors to Consider

Duration and exposure in humans

– Studies should be performed for pharmaceuticals where clinical use is expected for at least 6 months

– Studies should be performed where drug is used intermittently for treatment of a chronic or recurrent condition

ICH S1A
Requirement for Carcinogenicity Studies
Pharmaceuticals
Factors to Consider

Cause for concern

– Carcinogenic potential in product class considered relevant for humans
– Structure activity relationship
– Evidence of preneoplastic lesions
– Long term tissue retention of drug or metabolite

ICH S1A
Requirement for Carcinogenicity Studies
Pharmaceuticals
Factors to Consider

Genotoxicity

• Unequivocal genotoxic compounds do not require a carcinogenicity study
  – Presumed to be trans-species carcinogens
  – Imply a human hazard

• Single positive genotoxicity assay does not necessarily imply a human genotoxic hazard

ICH S1A
Requirement for Carcinogenicity Studies

Pharmaceuticals

Factors to Consider

Indication and Human Population

• Carcinogenicity studies generally needed for application for marketing approval
  – Post approval submission may be acceptable if drug is for certain serious diseases
  – Studies may not be required if life expectancy is short (i.e. less than 2-3 years)

• Studies generally not needed prior to large clinical trials
  – Unless there is concern for patient population

ICH S1A
Requirement for Carcinogenicity Studies
Pharmaceuticals
Factors to Consider

Route of exposure

• Route of exposure should be the same as clinical route. However:
  – Carcinogenicity studies are required by only one route if similar metabolism and systemic exposure is demonstrated for the different routes

ICH S1A
Requirement for Carcinogenicity Studies
Pharmaceuticals
Factors to Consider

Extent of systemic exposure

- Systemic carcinogenicity studies may not be required for optical products if
  - Poorly absorbable
  - No cause for concern

ICH S1A
Requirement for Carcinogenicity Studies
Pharmaceuticals
Factors to Consider
Endogenous peptides and proteins

- Determine need for assessment based on S1A
- Design strategy to address carcinogenicity potential; use weight of evidence (WOE) approach based on all available information
  1. If WOE supports concern; rodent bioassay is not warranted. Address by
     - Product Labeling
     - Risk management practices

ICH S1A; ICH S6 (NOTE: Revised June 2011)
Requirement for Carcinogenicity Studies

Pharmaceuticals

Factors to Consider

Endogenous peptides and proteins (continued)

• Design strategy to address carcinogenicity potential; use weight of evidence (WOE) approach based on all available information

2. If weight of evidence is unclear

• Sponsor should propose additional studies to mitigate mechanism-based concern

ICH S6 (NOTE: Revised June 2011)
Requirement for Carcinogenicity Studies
Pharmaceuticals
Factors to Consider
Endogenous peptides and proteins (continued)

Rodent bioassays with homologous products are generally of limited value to assess carcinogenicity

ICH S6 (NOTE: Revised June 2011)
Predicting Carcinogenicity

• Great interest in predicting carcinogenicity study results
  – Effect on product viability
  – Cost and time to perform a carcinogenicity study

• Multiple attempts to broadly predict carcinogenicity but none are accepted today
Predicting Carcinogenicity

Observations that Increase Probability of Carcinogenicity

• Genotoxicity carries a high liability for potential carcinogenicity
  – Rarely an issue since genotoxic agents are dropped from development

• Prolonged increase in cell proliferation increases probability of tumor response
  – Thyroid hyperplasia
  – Enhanced prolactin secretion
  – Renal tubular injury related to alpha-2u-globulin accumulation

• Increase in hyperplasia in chronic toxicity studies
Planning for Carcinogenicity Study
Planning for Carcinogenicity Study

• Planning for carcinogenicity studies is frequently given belated consideration

• Factors that should be considered at beginning and throughout toxicological assessment of molecule
  – Selection of species/strain
  – Metabolic profile compared to humans
  – Exposure profile
  – Sites of tissue injury
Planning for Carcinogenicity Study

Recommendation:

• Schedule data review 6 to 12 months prior to projected start of carcinogenicity study to assess data gaps
  – Toxicity data in animals and humans
    • Sites of tissue injury
    • Understanding of mechanism of injury
  – Exposure data in animals and humans
  – Metabolic profiles in animals and humans
Study Design
(2-year study)
Study Design
Species and Strain Selection

Rat and mouse generally used

• Rat considered more sensitive than mouse (ICH S1B)

• Other species may be used based on metabolism or biological considerations
  – Hamsters
  – Marmosets
  – Macaca monkeys
  – Dogs
Study Design
Species and Strain Selection

Animals in the carcinogenicity study should be same as in the pre-carcinogenicity program

- Species
- Strain
- Source

Commonly used strains
- Rats
  - Sprague Dawley
  - Wistar Han
  - F344
- Mouse
  - CD-1 Swiss
  - B6C3F1
Study Design
Species and Strain Selection

Commonly used strains (Frequent compound use, location)

• Rats
  – Sprague Dawley (Pharmaceutical, US)
  – Wistar han (Pharmaceutical, Europe)
  – F344 (Chemical and Pesticide, US and Europe)

• Mouse
  – Swiss (Pharmaceuticals, US and Europe)
  – B6C3F1 (Chemical and Pesticides, US and Europe)
Study Design
Route of Administration

Relevant mode of administration should be used

• Oral pharmaceutical = gavage
• Dermal pharmaceutical = dermal
• Air contaminant = inhalation
• Water pollutant = drinking water
• Dietary contaminant = feeding
Study Design
Route of Administration

- Gavage versus feed administration can result in very different toxicity and carcinogenicity profile
  - Alter MTD
  - Different Cmax
  - Metabolism may be altered due to saturation of metabolism with high exposure at Cmax in gavage study
Study Design
Diet Restriction

• Diet restriction (70-75% of ad libitum) has been used in carcinogenicity studies

• Value of food restriction
  – Increased survival
  – Decreased spontaneous disease incidence e.g. spontaneous nephropathy

• Limitation
  – Increased cost
Study Design
Diet Restriction

Pre-carcinogenicity studies must utilize diet restriction if considered for carcinogenicity study

• Diet restriction may increase MTD by 2 to 4X
• Toxicokinetics may be affected although it is frequently unchanged
Study Design

Number of Groups

- Number of groups will vary depending on objective and preceding toxicity data

<table>
<thead>
<tr>
<th>Vehicle 1</th>
<th>Vehicle 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Dose</td>
<td>Middle Dose</td>
</tr>
<tr>
<td>High Dose</td>
<td></td>
</tr>
</tbody>
</table>
Study Design
Dose Selection

• Doses selected based on objective of study
Issues in the Design and Interpretation of Carcinogenicity Studies in Rodents

Approaches to Dose Selection


Rodent Carcinogenicity Studies Dose Selection and Evaluation (US EPA 2003)

Dose Selection for Carcinogenicity Studies of Pharmaceuticals (ICH S1C 1997; Revised 2008)
Study Design
Dose Selection- Pharmaceuticals

• “The objectives of carcinogenicity studies are to identify a tumorigenic potential in animals and to assess the relevant risk in humans” ICH S1B

• Dose selection has been standardized through the ICH process

• Dose selection guideline first developed in 1994 with subsequent revisions

• Current ICH guideline is S1C(R2) revised in March 2008
Study Design

Dose Selection - Pharmaceuticals

• Carcinogenicity studies typically have 3 dose groups plus one or more control groups

• High dose has traditionally been selected based on a Maximum Tolerated Dose

• Doses are selected based on 3 month or 6 month toxicity studies that have defined multiple toxicity parameters
Study Design
Dose Selection - Pharmaceuticals

Considerations for “Dose-Ranging Studies”

- Metabolic profile in selected rodent species/strain should be as similar as possible to humans
- Study data must be available from both male and female animals
- Data required from 90-day studies
- Dosing schedule and regimen should be based on clinical use
- Toxicity profile and dose-limiting toxicity should be characterized
- Changes in metabolite profile and changes in enzyme activity should be established

ICH S1C(R2)
Study Design
Dose Selection - Pharmaceuticals

Selection of high dose (6 approaches)
• Toxicity based endpoints (MTD)
• Pharmacokinetic endpoints (25-fold AUC ratio)
• Saturation of absorption
• Pharmacodynamic endpoints
• Maximum feasible dose
• Limit dose

• Additional endpoints

ICH S1C(R2)
Study Design
Dose Selection- Pharmaceuticals

Toxicity endpoints in high dose selection

• Continue use of the MTD
• MTD is defined in ICH as a dose that is expected to “produce a minimum toxic effect over the course of the carcinogenicity study”
• Factors for consideration:
  – No more than 10% decrease in body weight gain
  – Target organ toxicity
  – Significant alterations in clinical pathology
Study Design
Dose Selection - Pharmaceuticals

Pharmacokinetic endpoints

• Selection of high dose may be based on a “...25 to 1 ratio of rodent to human plasma AUC of parent compound and/or metabolite”

• Approach is very useful but complex in application
Study Design
Dose Selection- Pharmaceuticals

Factors that require consideration in the use of 25-fold exposure approach for setting high dose

• Adequate animal TK and human PK data should be available for parent and metabolite
  – Frequently the maximum recommended human dose or human PK at this dose is not fully defined when a carcinogenicity study must be initiated

• Similarities of metabolism may be debatable

• Selection of parent or parent and metabolite as the basis for comparison may not be clear

• Protein binding must be considered since the 25-fold should be based on free drug
Study Design
Dose Selection- Pharmaceuticals

Application of a pharmacokinetic approach is best utilized when:

• Recommended human dose is clearly defined
  – Dose will not change for another indication

• Minimal metabolism occurs in humans and animals
  – A large number of metabolites complicates the application of this approach

• Minimal inter-individual variability in human exposure

• The animal to human AUC ratio is much greater than 25
  – Relatively small changes in PK from ongoing studies may change the ratio to less than 25
Study Design
Dose Selection - Pharmaceuticals

Saturation of absorption

• High dose should not exceed the maximum absorption

Drug Concentration, plasma

mg/kg 10 30 90 270 810

mg/kg

Drug Concentration, plasma
Study Design
Dose Selection- Pharmaceuticals

Pharmacodynamic endpoints

• The pharmacologic effect should preclude use of a higher dose
  – Inhibition of blood clotting
  – Hypotension
  – Neuroactive agents
Study Design
Dose Selection- Pharmaceuticals

Maximum feasible dose

- 5% of diet has historically been a maximum feasible dose

- May also be limited by maximum gavage volume (generally 10 mL/kg)
  - Results from poor solubility
  - Other vehicles should be considered

- Acceptance of pharmacokinetic endpoints should reduce use of Maximum Feasible Dose
Study Design
Dose Selection- Pharmaceuticals

Limit dose

• Limit dose is 1500 mg/kg/day if the maximum recommended human dose is not greater than 500 mg/day

• Rodent systemic exposure should be at least 10X greater than human exposure at the human therapeutic dose
Study Design
Dose Selection - Pharmaceuticals

Selection of middle and low doses
• Should be selected to provide insight into relevance of study results to humans.
  – Should not be specific fractions of the high dose
• Factors to consider
  – Human exposure
    • Ideally low dose should provide at least a small multiple of the human exposure
  – Linearity or lack of linearity of the rodent exposure curve
  – Mechanistic considerations
  – Threshold of minimal effects in dose range studies
    • Minimal necrosis
    • Enhanced cell proliferation
  – Alteration in rodent physiology
Study Design
Control Groups

• Single control group
• Two control groups
  – Duplicate
  – Vehicle versus non-vehicle
Study Design
Control Groups

• Single control group
  – Good science mandates a control group
  – Single control group is acceptable
  – Variation in background tumor incidence occurs in carcinogenicity studies
    • Within a laboratory in a similar time period
    • “Drift” in background tumor incidence over time
Study Design

Control Groups

• Two control groups
  – Duplicate (most frequently used)
    • Increases the total number of control animals to assist in statistical evaluation
    • Provides a backup control group in case of poor survival in one control group
    • Provides an internal control on the control group in case one control group has an unusually high or low incidence of background tumors
Study Design
Duplicate Control Groups

• Examples of differences between Sprague Dawley rat control groups

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Control 1</th>
<th>Control 2</th>
<th>Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal Pheochromocytoma</td>
<td>7/60</td>
<td>14/60</td>
<td>Male</td>
</tr>
<tr>
<td>Skin fibroma/dermal fibroma</td>
<td>6/60</td>
<td>2/60</td>
<td>Female</td>
</tr>
<tr>
<td>Thyroid C cell adenoma</td>
<td>8/50</td>
<td>1/49</td>
<td>Female</td>
</tr>
</tbody>
</table>

Adapted from: Toxicologic Pathology 33:283-291, 2005
Study Design
Control Groups

• Two control groups
  – Duplicate (most frequently used)
  – Vehicle versus non-vehicle
    • Uncommonly used
    • Used when a novel vehicle is included e.g. to increase solubility to increase dose
Study Design

Group Size

• Common group size ranges from 50 to 70 animals/group

• Goal: Assure adequate number of animals survive to study termination
  – Histological evaluation
  – Statistical analysis

• Group size should be based on survival history
  – Species/strain from the source to be utilized
  – Recent historical data from the laboratory
Study Design
Clinical Pathology

• Clinical pathology evaluation generally not included at end of study
  – Non-neoplastic effects of compound previously determined in chronic multi-dose studies
  – Complications of spontaneous disease e.g.
    • Liver tumors
    • Chronic kidney disease
Organ Weights

• Organ weights are not collected in carcinogenicity studies

• Organ weights at study termination are not helpful due to effects of:
  – Neoplasms
    • Spontaneous
    • Compound induced
  – Non-neoplastic spontaneous disease
  – Debilitation
Study Design
Tissue Collection

• STP minimum core list of recommended tissues (Tox Path 31: 252-253, 2003) includes:
  – 40 tissues (see reference)
  – Organ or tissues with gross lesions
  – Tissue masses
  – Additional tissues based on study design e.g.:
    • Nasal cavity, larynx and tracheobroncial lymph nodes in inhalation study
    • Administration sites for IV or skin application studies
Study Design
Histopathology

• Histological diagnosis of tumors is the ultimate basis for determining carcinogenicity in an appropriately designed and performed study

• Important issues:
  – Collection of appropriate tissues
  – Plan for reading tissues from “unscheduled deaths”
  – Determine approach for pathologist evaluation
  – Pathology peer review
Transgenic Mouse Studies

Alternative Carcinogenicity Studies
Transgenic Mouse Studies

• Currently, “...one long term rodent carcinogenicity study, plus one other study ...that supplements the long term carcinogenicity study” (ICH S1B, 1997)
  – Initiation-promotion studies
  – Transgenic mouse studies
  – Neonatal rodent studies

• Transgenic mice are now accepted in place of the 2-year mouse study

• More than a decade of refinement of the approach to using transgenic mice
Transgenic Mouse Studies

• Approximately 20% of all proposed mouse studies used transgenic mice in period from 2002-2010

• Appears to be a trend to the use of transgenic mice although FDA transgenic mouse protocol submissions have remained constant at 20%
  – Large companies using transgenic models more readily than small companies

• 40% of proposed mouse studies used transgenic mice in 2011
Transgenic Mouse studies

Primary Reasons for Acceptance of Transgenic Mouse Models

High level of comfort on part of sponsors and regulatory agencies

– No significant technical problems with studies
  • Survival
  • Background tumor incidence
  • Results of WT control
  • Results of positive control
  • Diagnostic issues with tumors
Transgenic Mouse studies
Primary Reasons for Acceptance of Transgenic Mouse Models

No longer a concern that transgenic models may produce a high rate of false positives

– Early assessment of transgenic studies indicated a good record to predict known or suspected human carcinogens (Environmental Health Perspectives 111(4), 444-454, 2003)

– Recent transgenic mouse submission to FDA have identified very few positive results
Transgenic Mouse studies

Models may be currently underutilized
Transgenic Mouse Studies

Today the predominant mouse models are:

- P53+/-  (P53 KO)
  - Accepted in US only for genotoxic compounds
  - Accepted in Europe for both genotoxic and non-genotoxic compounds

- TgrasH2 (Multiple copies of human ras gene)
  - Preferred model in US for non-genotoxic compounds
Transgenic Mouse Studies

Other transgenic mouse models

– Tg.AC
  • Used only for products with dermal application
  • Therefore infrequently used
  • Supplier no longer provides this mouse

– XPA-/-
  • Was evaluated for possible future use
  • Not routinely used
  • Appears to be little to no interest currently
Transgenic Mouse Studies
Special Study Design Features

• Treat for 6 months
  – Spontaneous tumors will develop after this time
• Group size: 25 animals
• MTD only accepted approach to high dose selection
  – Wild type mice used in dose selection studies to set MTD
• Positive control should be included in the study unless reproducibility of study results are established for the laboratory
• Standard histopathology criteria used for diagnosis of tumors
Review of Study Plan
Review of Study Plan

• Two levels of review
  – Internal review
  – Regulatory review
Review of Study Plan

• Internal
  – Should include a full review of study plan with special emphasis:
    • Objective
    • Doses selected
  – Review should be performed by persons familiar with:
    • Toxicology program of the molecule and related molecules if relevant
    • Design and performance of carcinogenicity studies
Review of Study Plan

- Regulatory review (FDA review by CAC)
  - Carcinogenicity studies are the only toxicology studies that are eligible for “special protocol assessment” under PDUFA
  - Primary review responsibility is with the division but submissions are routinely sent to CAC
  - Review covers study type, doses employed and other design issue

Guidance for Industry, Carcinogenicity Study Protocol Assessment, Food and Drug Administration CDER
Review of Study Plan
Regulatory review (FDA review by CAC)

• Information to be included in review package appropriate for the study design
  – Carcinogenicity study protocol
  – Study report for pre-carcinogenicity studies
  – Metabolic profiles in humans and carcinogenicity study species. Ideally in vivo; in vitro acceptable
  – Toxicokinetic data for parent and each major human metabolite
  – Exposure for parent drug and major metabolites from clinical trials at the “maximum recommended human dose”
Review of Study Plan
Regulatory review (FDA review by CAC)

• Information to be included in review package appropriate for the study design (continued)
  – Plasma protein binding in humans and animals for parent drug and major human metabolites
  – Summary of genotoxicity study results for parent and major human metabolites.
Review of Study Plan
Regulatory review (FDA review by CAC)

• Submission process
  – Notify review division 30 days prior to submission
  – Submission should be clearly marked
    • “REQUEST FOR SPECIAL PROTOCOL ASSESSMENT”
    • Carcinogenicity protocol
Design of Carcinogenicity Study

Sequential Checklist

- Determine need for study
- Clarify study objective(s)
- Assemble all available data for review
- Determine missing data
- Select species
- Determine basis for selection of high dose
- Select and justify high dose
- Determine basis for selection of low dose
- Select and justify low dose
- Determine potential problems
- Prepare protocols and supporting documents
- Critical colleague review
- Regulatory agency review
Study Oversight
Study Oversight

• Carcinogenicity study requires greater monitoring than other animal studies
  – High investment in study
  – Usually critical timeline related to submission for marketing approval
Study Oversight

• Items for special attention:
  – Survival

• Important to assure that there are adequate animals available for statistical analysis at end of study
  – Ideally should have 15 to 20 animals in each group at end of 2 years
  – If survival is reduced, early termination should be considered but only with input and concurrence from FDA.
Study Oversight

• Items for special attention:
  – Survival
  – Timely collection of tissue from early deaths
    • Autolysis of tissue may prevent histopathological diagnosis resulting in:
      – Reduced animals for evaluation thereby impacting statistics
      – Raise questions regarding other aspects of study performance
  – Adequate collection of tissue from all animals
    • Lack of tissue reduces the number of animals examined
Study Oversight

• Dealing with reduced survival takes time and therefore requires an aggressive approach

• Communication path and decision making process
  – CRO notification of sponsor
  – Internal discussions of sponsor staff and management
  – Preparation of submission of data and request for early termination to FDA
  – FDA consideration of request and preparation of response
  – Scheduling early sacrifice at CRO
Study Oversight

• Pathology Peer Review
  – Not required but highly recommended
  – Requires an experienced pathologist
  – Process should be defined in advance but typically includes:
    • Review of all tumors and hyperplastic lesions that might be considered tumors
    • Review of all target organs
    • Review of all tissues from a subset of control and high dose groups
Statistics
Statistics

• Statistical evaluation:
  – Should be considered as part of the study design
  – Focuses on
    • Tumor incidence
    • Time to tumor appearance
    • Considers survival effects
Interpretation of “Positive” Results for Assessing Human Safety
Interpretation of “Positive” Results for Assessing Human Safety

First step: Determine the basis of the tumor response in animals. Use all currently available information:

- Genotoxicity
- Dose response
- Toxicokinetics
- Hormonal imbalance
- Enzyme induction
- Altered physiological state
- Cell death/proliferation
Interpretation of “Positive” Results for Assessing Human Safety

Second step: Seek a mechanistic understanding of tumor response.

• Literature review
• Special studies
  – Timing of special studies
  – Selection of special studies
  – How much information is enough
Mechanistic Understanding of Tumor Response

Several rodent tumors considered not relevant for humans IF adequate data is available

- Male rat kidney tumors associated with alpha-2-\(u\)-globulin
- Mammary tumors associated with prolactin production in rats
- Thyroid tumors in rats associated with several perturbations of thyroid hormone metabolism e.g. increased glucuronidation
Mechanistic Understanding of Tumor Response

Cellular changes as related to dose response
- Foci of cellular alteration in liver
- Cell proliferation
- Apoptosis

Biochemical measurements that are frequently contemplated depending on tumor type
- Plasma hormone levels e.g. TSH, prolactin
- Growth factors
- Alpha-2u-globulin in kidney tubules
- Tissues enzyme activities

Growth factor mediated carcinogenesis is becoming more common

(Examples from ICH S1B)
Interpretation of “Positive” Results for Assessing Human Safety

Third step: Perform a formal human risk assessment

• Is mechanism of tumor response in animals likely to occur in humans?
Regulatory Implications of a “Positive” Study
Regulatory Implications of a “Positive” Study

• Implication can be very different depending on whether the molecule is a pharmaceutical or chemical/pesticide.
  – Pharmaceutical considers a risk benefit comparison
  – Chemicals /pesticides consider only risk

• One third of drugs in PDR that have carcinogenicity data are either positive or equivocal (Mutat Res 488:151-169, 2001)
ICH Guidelines

• Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals  S1A

• Testing for Carcinogenicity of Pharmaceuticals  S1B  http://www.ich.org/LOB/media/MEDIA490.pdf

• Dose Selection for Carcinogenicity Studies of Pharmaceuticals  S1C(R2)

• Preclinical Safety Evaluation of Biotechnology–Derived Pharmaceuticals S6
FDA Guidance

• Carcinogenicity study protocol submission
  (http://www.fda.gov/cder/guidance/4804fnl.pdf)

• Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals.
  (http://www.fda.gov/cder/guidance/815dft.pdf)
Transgenic Mouse Models
Key References

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History of Carcinogenesis Evaluation

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https://www.surveymonkey.com/s/VNHVGKT