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Practical Aspects of Preparing and Filing Rodent Carcinogenicity Protocol Submissions to the United States Food and Drug Administration through the Special Protocol Assessment Procedure

Mike Luksic, Kathryn Bibeau, Geoff Goodfellow and Jon Daniels
Cantox Health Sciences International

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The purpose of this presentation is to introduce the United States Food and Drug Administration (FDA)'s Special Protocol Assessment Procedure in relation to carcinogenicity protocol submissions. The background, regulations, and guidance documents concerning this procedure will be discussed as well as the practical aspects such as what to submit, how to submit, and where to submit. In accordance with the Prescription Drug User Fee Act (PDUFA) Reauthorization (1997), FDA will follow the Special Protocol Assessment procedure for reviewing carcinogenicity protocols at the request of a Sponsor. The agency will evaluate the protocol to assess whether the design is adequate to meet scientific and regulatory requirements. This assessment includes a review of the basis for dose. Written recommendations are to be provided to the Sponsor within 45 days of receipt of the protocol. The major advantages for the Sponsor include reduced risk (*i.e.*, FDA buy-in to the proposed study) and potentially significant savings in terms of time and money (*i.e.*, by reducing the likelihood that a study will need to be repeated). Finally, case studies will be presented which identify common issues with carcinogenicity protocol submissions and outline how FDA's assessment may differ from the Sponsor's standpoint.

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PRESENTATION OUTLINE

- Basics – Regulations and Guidance Documents – What? Who? Why?
- Practical Aspects – How? When? Where?
- Case Studies – Potential Issues

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BASICS

WHAT?

- Prescription Drug User Fee Act (PDUFA) Reauthorization, 1997:
  - Special Protocol Assessment
  - 45-Day Review

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BASICS

WHAT?

- Relevant Guidance Documents – FDA:
  - Special Protocol Assessment, 2002
  - Carcinogenicity Study Protocol Submissions, 2002
  - Dose Selection for Carcinogenicity Studies of Pharmaceuticals, 1995

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BASICS

WHAT?

- Relevant Guidance Documents - ICH:
  - S1B Testing for Carcinogenicity of Pharmaceuticals, 1997
  - S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals, 1994
  - S1C(R) Addendum – Addition of a Limit Dose and Related Notes, 1997

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BASICS

WHO?

- According to the FDA Manual of Policies and Procedures (MaPPs):
  - Reviewing Division initiates review
  - CAC reviews submission
  - CAC provides recommendations to Division
  - Division provides CAC recommendations to Sponsor

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BASICS

Who?

- **Associate Director CDER Pharmacology/Toxicology:**
  - Dr David Jacobson-Kram
  - Highly involved in alternative transgenic models

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BASICS

Why?

- **Reduce Risk**
- **Expensive Studies (up to $1,500,000 US each)**
- **Save Time (~ 3 years from start to finish)**

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PRACTICAL ASPECTS

HOW?

- **Rodent Carcinogenicity Testing Options:**
  1. Rat and Mouse 2-Year Bioassays
  2. Rat 2-Year Bioassay and Transgenic Mouse Model (p53+/-, TgAC, rasH2)

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PRACTICAL ASPECTS

HOW?

- **Special Protocol Assessment Procedure:**
  - Notify Review Division that protocol is forthcoming 30 days BEFORE submitting
  - Submit protocol or study design, relevant background, and questions
  - Each protocol should be a separate submission
  - CAC and Review Division respond in 45 days (or less)

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PRACTICAL ASPECTS

HOW?

- **Study Design Features :**
  - Number of Animals/Groups
  - Parameters to be monitored (e g , mortality, body weights)
  - Toxicokinetics
  - Tissue list (Bregman et al , 2003, Jacobs et al , 2003)
  - Proposed dose levels
  - Design must be specific to drug

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PRACTICAL ASPECTS

HOW?

Basis for Selection of the High Dose [see ICH S1C S1C(R)]

1. Maximum Tolerated Dose
2. 25-Fold AUC Ratio (rodent human)
3. Saturation of Absorption
4. Dose-Limiting Pharmacodynamic Effects
5. Maximum Feasible Dose
6. Other case-by-case basis
7. Multiple acceptable criteria

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PRACTICAL ASPECTS

HOW?

- **Basis for Selection of Mid and Low Doses**
  - To provide information to help in assessing the relevance of the findings to humans
  - Integration of rodent and human pharmacokinetic, pharmacodynamic, and toxicity data

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PRACTICAL ASPECTS

Useful Data for Protocol Review					
Endpoint	Tox	Chemo-tox	Meta-bolism	AUC rodent	AUC human
Toxicity (MTD)	√	A	M	N/A	N/A
25xAUC	√	√	√	√	√
Saturation	√	A	M	√	N/A
MFD	√	A	M	N/A	N/A
Limit Dose	√	√	√	√	√
PD	√	A	M	N/A	N/A

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PRACTICAL ASPECTS

HOW?

- **Key Toxicity Endpoints – Interpreting Data**
  - Mortality
  - Body weight gain (>10% decrease)
  - *Target organ toxicity*
  - Histopathology
  - Clinical pathology

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PRACTICAL ASPECTS

HOW?

- **Other Design Features:**
  - Statistics (FDA, 2001)
  - But FDA will typically not address the proposed statistical evaluation, as it does not affect initiation of the studies

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PRACTICAL ASPECTS

WHEN?

- **Carcinogenicity Studies (when required to support registration) usually submitted:**
  - With New Drug Application (most chronic indications)
  - Phase IV Commitment
- **Carcinogenicity protocol submission at least 3 *years before applying for marketing approval***

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PRACTICAL ASPECTS

WHERE?

- **Carcinogenicity studies – Large investment (time and $$)**
  - Reputable testing facility
  - Good Laboratory Practices
  - Carcinogenicity testing experience
  - Carcinogenicity database
  - Computer system (e g , Xybrian)

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CASE STUDIES

1. **Small molecule**
   - Basis for HD pharmacokinetic (25XAUC)
2. **Peptide**
   - Basis for HD toxicity enpoints
3. **Immunosuppressant**
   - Basis for HD toxicity endpoints

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CASE STUDIES - 1

- **Small molecule**
- **Proposed Basis for Dose Selection:**
  - Pharmacokinetic Endpoints
    - High Dose 25xAUC
    - Mid Dose 10xAUC
    - Low Dose 1xAUC

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CASE STUDIES - 1

- **Types of Data Submitted:**
  - 26-week rat
  - 13-week mouse
  - Metabolism (rat, mouse, human)
  - Toxicokinetics (rat, mouse)
  - Pharmacokinetics (human)
  - *Plasma protein binding (rat, mouse, human)*
  - Genotoxicity

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CASE STUDIES - 1

- **Critical Data:**
  - Human pharmacokinetics
  - Rodent toxicokinetics
  - Parent and metabolites
    - Used radiolabeled test article
  - Plasma protein binding (bound vs unbound)

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CASE STUDIES - 1

- **Supporting Data:**
  - 26-week rat (up to 200 μg/kg/day)
    - *Middle dose for carcinogenicity based on low dose in 26-week rat*
  - 13-week mouse (up to 2500 μg/kg/day)
    - Middle dose for carcinogenicity based on low dose in 13-week mouse

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CASE STUDIES - 1

- **Proposed Basis for High Dose Selection:**
  - Human subjects = AUC 1 4 μg/mL•hr (at 0 72 μg/kg)
  - Proposed Therapeutic Dose – 0 48 μg/kg
    AUC estimate 1 4 μg/mL•hr (0 48 μg/kg÷0 72 μg/kg) = 0 9333 μg/mL•hr
    25XAUC = 25x0 933 μg/mL•hr
    = 23 3 μg/mL•hr

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CASE STUDIES - 1

- **Data (single dose):**
  - Mice – 12 5 μg/kg = AUC 20 μg/mL•hr
  - Mice – 25 μg/kg = AUC 40 μg/mL•hr
    Estimate AUC 23 3 μg/mL•hr ≅ 37 μg/kg
- **Data (single dose):**
  - Rats – 25 μg/kg = AUC 20 μg/mL•hr
  - Rats – 50 μg/kg = AUC 40 μg/mL•hr
    Estimate AUC 23 3 μg/mL•hr ≅ 18 6 μg/kg

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CASE STUDIES - 1

- **Issues:**
  - Based on single dose
  - Method did not identify parent vs metabolite (total)
  - Did not use proposed therapeutic high dose to determine AUC
  - Doses for 25XAUC extrapolated

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CASE STUDIES - 1

- FDA Response
  - Did not concur with PK endpoint for high dose selection Instead
    - MICE
      - Based on estimated MTD in 13-week mouse study
      - MTD between 50 and 500 μg/kg/day
      - Basis for MTD diarrhea, histopathological changes in GI tract
      - Added a dose group

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CASE STUDIES - 1

- FDA Response
  - RATS
    - Based on estimated MTD in 26-week rat study (0 8 40 200 μg/kg/day) and findings in 4-week rat study
    - MTD 200 μg/kg/day for males, >200 μg/kg/day for females
    - Basis for MTD decreased body weights and histopathological changes in stomach and diarrhea in 4-week study at 500 μg/kg/day

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CASE STUDIES - 1

Summary of Proposed Doses (μg/kg/day) - Mice		
	Sponsor	FDA
Endpoint	PK	Toxicity
High	40	250
Mid	16	100
Low	1.6	37 5
Low 2	-	12.5

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CASE STUDIES - 1

Summary of Proposed Doses (μg/kg/day) - Rats		
	Sponsor	FDA
Endpoint	PK	Toxicity
High	20	200
Mid	8	50
Low	0 8	10

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CASE STUDIES - 2

2) Peptide (Synthetic)

- 2-Year Rat Study
- Mouse Study – Alternate Model p53 (not discussed here)

<u>Rat Study</u>

- **Proposed Basis for Dose Selection:**
  - **Toxicity Endpoints**

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CASE STUDIES - 2

- **Types of Data Submitted:**
  - Dose escalating study in rats
  - 14-day rat (daily)
  - 14-day rat (q2d)
  - 13-week rat (q2d)
  - Metabolism (rat, human)
  - Toxicokinetics (rat)
  - Plasma protein binding (rat, human)
  - Genotoxicity

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CASE STUDIES - 2

- Critical Data
  - 14-day rat (0, 0 0084, 0 05, 0 3 mg/kg/day)
  - 14-day rat (0, 0 24, 1 2, 6 mg/kg/q2d)
  - 13-week rat (0, 0.1, 0 6, 3 6 mg/kg/q2d)

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CASE STUDIES - 2

- **Supporting Data:**
  - Toxicokinetics (for mid and low doses)
  - Parent Plasma protein binding
  - Metabolism

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CASE STUDIES - 2

- *Proposed Basis for High Dose Selection*
  - 14-Day Rat Study (Daily Dosing)
    - MTD = 0 05 mg/kg/day based on decreased body weight gain (>10%)
  - *13-Week Rat Study (q2d)*
    - MTD < 0 1 mg/kg/q2d based on decreased body weight gain in all groups (>10%) [effect not statistically significant in females]

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CASE STUDIES - 2

- *Proposed Doses*
  - High Dose 0 05 mg/kg/day
  - Mid Dose 0 01 mg/kg/day
  - Low Dose 0 002 mg/kg/day

  Mid and low doses based on linearity of PK

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CASE STUDIES - 2

- Issues
  - Range-finding data q2d vs daily
  - Body weight effect somewhat transient (decrements were attenuated with study duration > 13 weeks)
  - No dose-limiting toxicity in females in the 13-week study

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CASE STUDIES - 2

- **FDA Response:**
  - Did not concur with dose selection Instead
    - Males 0 2, 0 6, 1 8 mg/kg/day based on significant body weight decrements
    - Females Additional dose range-finding study recommended

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CASE STUDIES - 2

Summary of Proposed Doses (mg/kg/day)		
	Sponsor	FDA
Endpoint	BW decrease	BW decrease Males only
High	0 05	1.8
Mid	0 01	0 6
Low	0 002	0.2

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CASE STUDIES - 3

2) Immunosuppressant

2-Year Rat Study

Mouse Study – Alternate Model p53 (not discussed here)

Rat Study

Proposed Basis for Dose Selection:

- **Toxicity Endpoints**
- **25XAUC Inappropriate due to severe toxicities in rodents *(Hastings, 2000) [Class-related literature]***

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CASE STUDIES - 3

- Types of Data Submitted
  - 28-day rat
  - 13-week rat
  - 26-week rat
  - Metabolism (rat, human)
  - Toxicokinetics (rat)
  - Pharmacokinetics (human)
  - Plasma protein binding (rat, human)
  - Genotoxicity

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CASE STUDIES - 3

- Critical Data
  - 28-day rat (0, 20, 50, 160 mg/kg/day)
  - 13-week rat (0, 5, 20, 50 mg/kg/day)
  - 26-week rat (0, 2 5, 5, 20 mg/kg/day)

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CASE STUDIES - 3

- **Supporting Data:**
  - Toxicokinetics – rats
  - Pharmacokinetics - human
  - Parent Plasma protein binding
  - Metabolism

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CASE STUDIES - 3

- **Proposed Basis for High Dose Selection:**
  - 26-Week Rat Study
    - Histopathological findings related to immunosuppression (thymic atrophy, decreased WBC)
      - MTD = 2 5 mg/kg/day in males
      - 5<MTD<20 mg/kg/day in females

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CASE STUDIES - 3

- **Proposed Doses:**
  - High Dose 2 5 mg/kg/day
  - Mid Dose 1 25 mg/kg/day
  - Low Dose 0 6 mg/kg/day

Mid and low doses based on linearity of PK

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CASE STUDIES - 3

- **Issues:**
  - No significant mortality or body weight effects
  - Higher AUCs in males than females
  - Proposed high dose is less than clinical dose (after adjustment for body surface area)

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CASE STUDIES - 3

- **FDA Response:**
  - Did not concur with dose selection Instead
    - Males 0 1, 0 5, 2 5 mg/kg/day based on known toxicities of this class (and progression of effects)
    - Females 0 5, 2 5,10 mg/kg/day based on gender differences in TK and toxicities

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CASE STUDIES - 3

Summary of Proposed Doses (mg/kg/day)			
	Sponsor	FDA	
Endpoint	Toxicity	Class Effects	
		Male	Female
High	2.5	2.5	10
Mid	1.25	0 5	2.5
Low	0 6	0.1	0 5

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CONCLUSIONS

- Make use of FDA Special Protocol Assessment
- Gain timely FDA input
- Reduce risk (time, $$) associated with 2-year bioassays
- Consider other jurisdictions

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