Peroxisome Proliferator-Activated Receptor Agonists:

Carcinogenicity Findings and Regulatory Recommendations

Jeri El Hage, Ph.D.
Div. of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research , FDA

Peroxisome Proliferator-Activated Receptors (PPAR)

- Nuclear hormone receptors that act as ligand-activated transcription factors
- Three PPAR subtypes – alpha, delta (beta) , and gamma receptors
- Ligand-activated PPAR receptor forms a heterodimer with retinoid X receptor (RXR)
- PPAR – RXR binds to PPRE (DNA response elements) to
- alter gene expression in a cell, developmental, and sex-specific manner

Tissue Expression of PPAR α, δ, and γ

PPAR α	PPAR δ/β	PPAR γ
Brown fat Liver Kidney Heart Diaphragm Skeletal muscle Immune syst. Intestine Retina	Ubiquitous Skeletal muscle Cardiac muscle	Adipose Colon Cecum Immune syst. Vasculature Bladder Spleen

Physiologic Roles of PPAR α, δ, and γ

PPAR α	PPAR δ	PPAR γ
Lipid catabolism Wound healing Peroxisome Prolifer.	Cell proliferation Embryonic implantation Adipocyte differentation. Myelination ??	Adipocyte differentiation Lipid storage Macrophage maturation Inflammation (-)

Potential Therapeutic Indications

- PPAR alpha agonists – dyslipidemia - decrease TG/ increase HDL
  - Approved drugs - Fibrates – fenofibrate, gemfibrozil
- PPAR gamma agonists – type 2 diabetes- improve insulin sensitivity
  - Approved drugs – Thiazolidinediones – rosiglitazone, pioglitazone
- PPAR dual agonists (alpha + gamma)- diabetes & dyslipidemia
- PPAR pan agonists (alpha/gamma/delta)-diabetes, dyslipidemia, obesity (metabolic syndrome)
- PPAR delta agonists – obesity, decrease gamma-mediated fluid accumulation and weight gain

Historical Perspective
PPAR Alpha Agonists and Rodent Carcinogenicity

- Extensive literature describes PPAR alpha- induced peroxisome proliferation and liver cancer in rodents, but human relevance disputed based on cross species differences in responsiveness and the clinical experience with fibrates.
- FDA experience - Significant peroxisome proliferation (2 – 5 –fold) and liver hypertrophy observed in monkeys treated with most compounds with potent PPAR alpha activity (alpha, dual , pan agonists).
- Pharmaceuticals in development 10 – 1000- fold more potent human PPAR alpha agonists than the fibrates.
- Many compounds in development display significant species differences in PPAR alpha potency (human >> mouse, rat) .

Carcinogenicity Findings for PPAR Agonists (Pharmaceuticals)

- Carcinogenicity study results for 11 compounds demonstrate that PPAR agonists are multi-species, multi-strain, multi-sex, multi-site carcinogens. Therefore, "probable human carcinogens" according to EPA and IARC criteria.
- Several sponsors discontinued drug development due to rodent tumor findings.
- European regulators convened Expert Working Group to review available rodent carcinogenicity data.
- Mechanistic data to explain mode(s) of action for tumor formation not available .
- Tumors sites are consistent with the known distribution of PPAR receptors.
- Spring 2004 - The Division of Metabolic and Endocrine Drug Products and CDER Executive Carcinogenicity Assessment Committee review the available rodent carcinogenicity data for the PPAR agonists (completed 2 year rodent bioassays) and develop recommendations to insure patient safety.

Tumor Findings with PPAR Gamma Agonists

Drug	Hemangio Sarcoma	Bladder	Lipoma/ Sarcoma	Liver	Other Tumors
A	Mice M, F		Rat M, F	Mice, F	
B			Rat M, F		
C		Rats M, F			Mice - Leiomyosarcoma cervix
D	Mice M, F		Rat M		Mice M, F Gallbladder adenoma
E	Mice M, F			Rats, F	Rat, M - stomach leiomyosarcoma

Tumor Findings with PPAR Dual Agonists

Drug	Hemangio Sarcoma	Bladder/ Renal	Fibro- Sarcoma	Lipoma/ Sarcoma	Liver	Other Tumors
F		Rat M,F		Rat-M	Rat F	Rat – testicular, mammary, thyroid -F
G	Mice M,F	Rat M,F	Rat, F		Mice M, F	Rat, F – mammary adenocarcinoma
H	Mice M,F	Rat M,F		Rat M, F Mice M, F		Mice, F – mammary Mice , M- stomach
I	Hamster M		Rat M, F		Rat M, F	Rat, F - thyroid
J	Mouse F	Rat M		Rat M, F		Mouse - gallbladder Rat- uterus
K	Mice M,F	Rat M,F				Rat – leukemia M, F Rat –Uterus

Common Tumor Findings for PPAR Agonists

Hemangioma/ hemangiosarcoma

Observed with 8/11 compounds - 3 gamma, 5 dual agonists

Findings in CD-1, B6C3F1 mice of both sexes and hamsters

Tumors at multiples sites - liver, spleen, skin, and adipose

Angiomatous hyperplasia/ angiectasis noted with several compounds in rodents and non-rodents

Common Tumor Findings for PPAR Agonists

Urinary bladder/ renal pelvic transitional cell carcinomas

Observed with 5/6 dual agonists and pioglitazone

Findings in Sprague Dawley, Wistar, and Fischer rats of both sexes.

Three PPAR agonists were also bladder tumor promoters in the rat initiation-promotion model (BBN- initiation/promotion model).

Bladder, renal pelvic and/or renal tubular hyperplasia commonly observed in rats, observed infrequently in dogs and monkeys

Other Tumor Findings with PPAR Agonists

- Lipoma/ liposarcoma (3 γ, 3 dual)- rats (5) , mice (1)
  - Gamma effect - adipocyte proliferation, differentiation all species
- Fibrosarcoma in skin (3 dual) - rats
- Mammary adenocarcinoma (3 dual) – mice, rats
- Gallbladder adenoma (1 γ, 1 dual)) – mice
- Leiomyosarcoma (2 γ, 1 dual) – mice – cervix, stomach;
  rats - stomach
- Sarcomatous tumors of renal tubules – 3 dual agonists

Clinical Implications of Carcinogenicity Results

- High prevalence of positive carcinogenicity findings with this class of compounds raises significant clinical safety concern.
- Sponsors have voluntarily discontinued development when tumors were observed at all doses and/or drug-related increases in tumors were observed with drug exposures in the therapeutic range
- Sponsors with ongoing Phase 3 programs have completed carcinogenicity studies and have demonstrated adequate safety margins between exposures associated with tumors and therapeutic exposures.

Implications of Rodent Carcinogenicity Findings for Phase 3 Product Development

Two-year rodent carcinogenicity studies must be completed and the draft reports submitted for agency review prior to clinical studies longer than 6 months in duration .

General statements describing the positive rodent carcinogenicity study findings for the PPAR agonists are recommended for inclusion in the Investigator Brochures and Informed Consent forms for all PPAR agonists.

Interpretation of Carcinogenicity Study Results

PPAR agonists submitted to date are not genotoxic in the standard ICH testing battery. Threshold doses can be established for compounds that produce tumors via non-genotoxic mechanism(s).

If tumors are observed at doses producing exposures in animals ≥ 10-fold therapeutic AUC exposures with the MRHD, then Phase 3 studies longer than 6 months may proceed. (Assuming comparable receptor transactivation potency in mice, rats and humans).

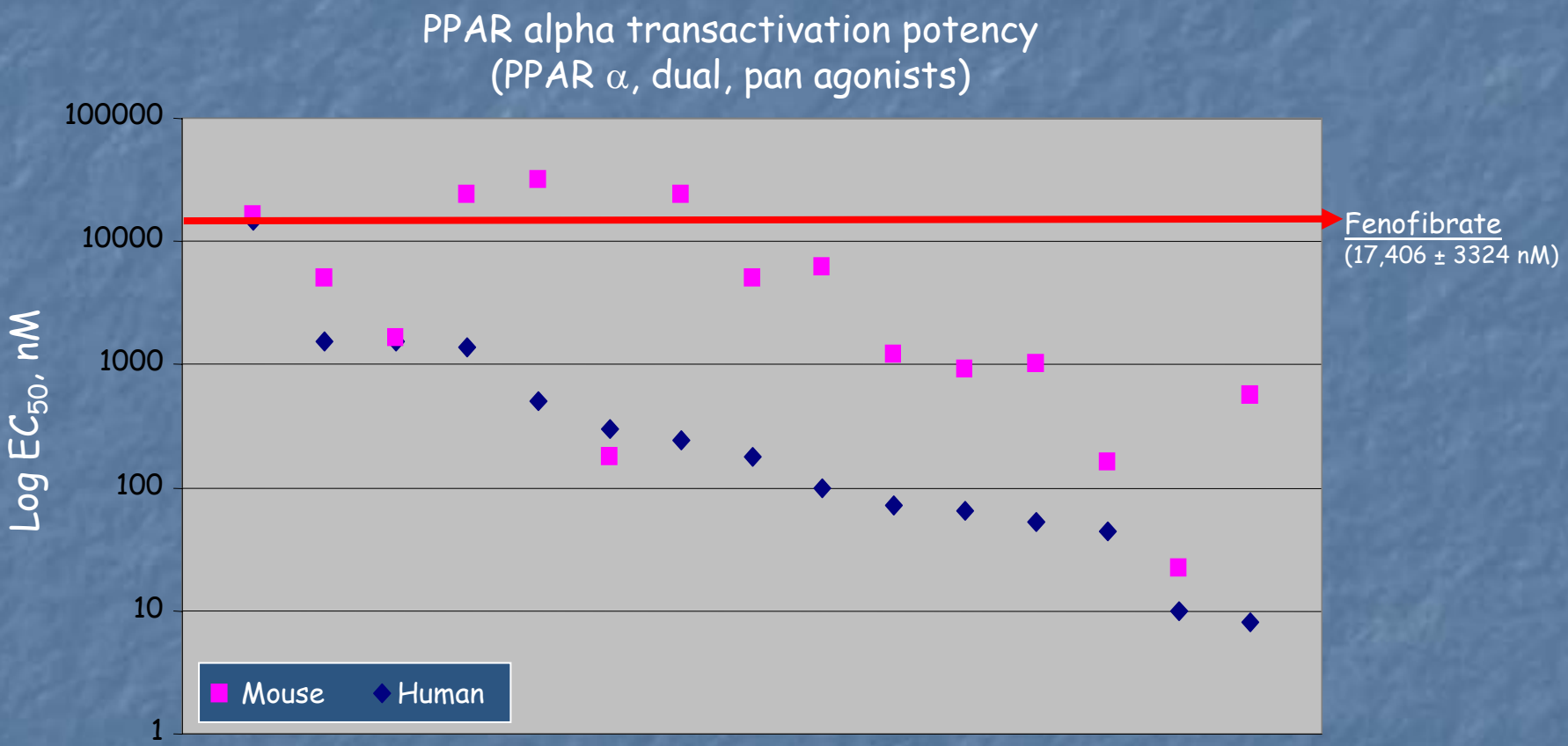
If tumors are observed at doses producing exposures in animals that are 1 to 9-fold clinical exposures OR all doses tested are associated with AUC exposures in animals < 10X the clinical exposure, carcinogenicity study results will be reviewed on a case by case basis by the Division and ECAC.

Conclusions

- The prevalence of PPAR agonist -induced tumor findings raise safety concerns for long-term clinical studies. Preliminary results from completed 2- year rodent carcinogenicity studies should be submitted for agency review prior to conducting clinical trials > 6 months in duration .

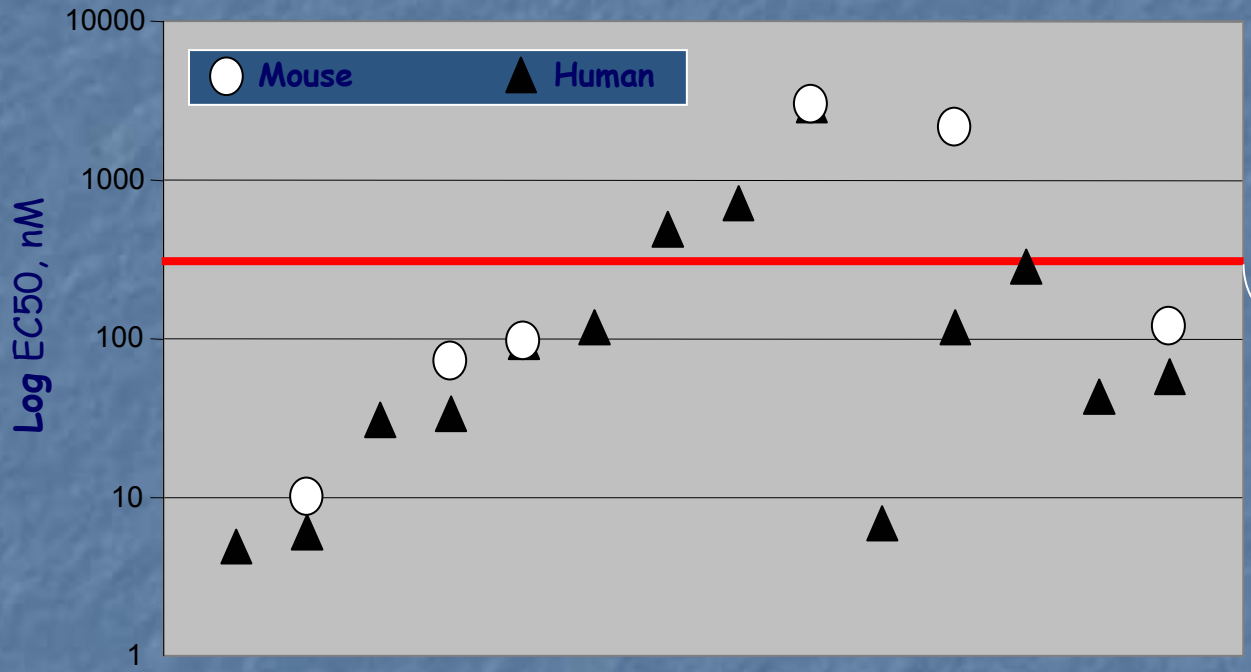
- Sponsors are encouraged to provide data on trans-species PPAR transactivation potency and mechanistic data to aid in the assessment of the human relevance of the rodent tumor findings.

- CDER Recommendations related to the clinical implications of the rodent tumor findings are consistent with those of other regulatory authorities.


PPAR alpha transactivation potency
(PPAR α, dual, pan agonists)
Log EC50, nM
100000
10000
1000
100
10
1
Mouse
Human
Fenofibrate
(17,406 ± 3324 nM)

Pio data is for human receptor,
Avg from 4 studies

PPAR gamma transactivation potency of PPAR gamma, dual, and pan agonists



Pioglitazone
500 nM Human

Vascular Tumor Incidences

Agonist	Sex	Control	LD	LMD	MD/HMD	HD
A	M F	6 6	2 6		7 17	16 13
D	M F	0 / 5 3 / 4	6 3		11 5	10 22
E	M F	2 1	3 1		4 8	5 5
G	M F	3 5	3 4		5 5	7 11
H	M F	0 0	6 4	3 8	8 7	9
I	M	0	0	8	4	7
K	M F	1 / 2 5 / 5	4 1	10 2	20 9	Early sacrifice

Bladder/ Renal Tumors

Agonist	Sex	Control	LD	LMD	MD/HMD	HD
C	M	0	2	7	7	6
	F	0	1	1	1	0
	F hyperplasia	0	2	5	3	11
F	M	1	0		3	24
	F	0	0		3	11
G	M	0	3		9	11
	F	0	1		4	7
H	M	0	6	8	12	5
	F	0	1	2	2	7
J	M	0	3	8	24	36
	F	0	0	0	0	0
K	M	1	0	2	3	14
	F	0	1	1	4	22