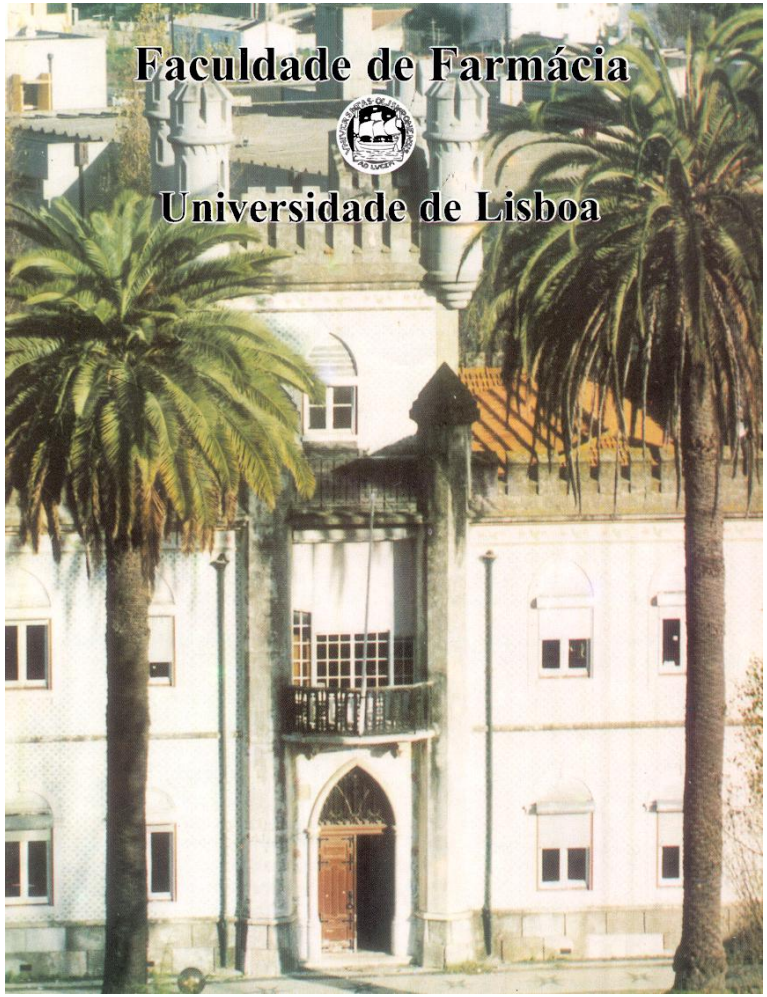
Recent Experience in Non-Clinical Assessment : Scientific Advice and Marketing Authorization Applications



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Expectations on Nonclinical Program

At the time of filing MAA

- MOST Concerns Should Have Been Addressed and/or Solved/Considered for Risk Management

- Major NC Problems Should NOT exist!

- **IN THE IDEAL DEVELOPMENT!**

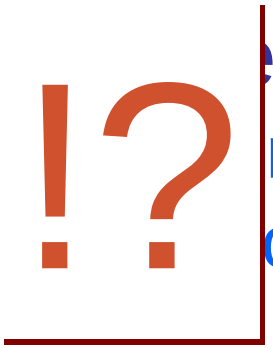
SINCE THE IDEAL DOES NOT EXIST …

Concerns often Persist on eg.

- Carcinogenicity / genotoxicity
- Genotoxic Impurities
- Reproductive Toxicity
- Hepatotoxicity
- …

However, Still Ar ed for MAAs

- Poor justificatic mal models
- Insufficient Kin oxicokinetics



EXAMPLES FROM MAAs
Case 1

- Carcinogencity Study**:**

-Liver adenomas/carcinomas

-Thyroid adenomas

- Additional findings

-liver enzyme induction

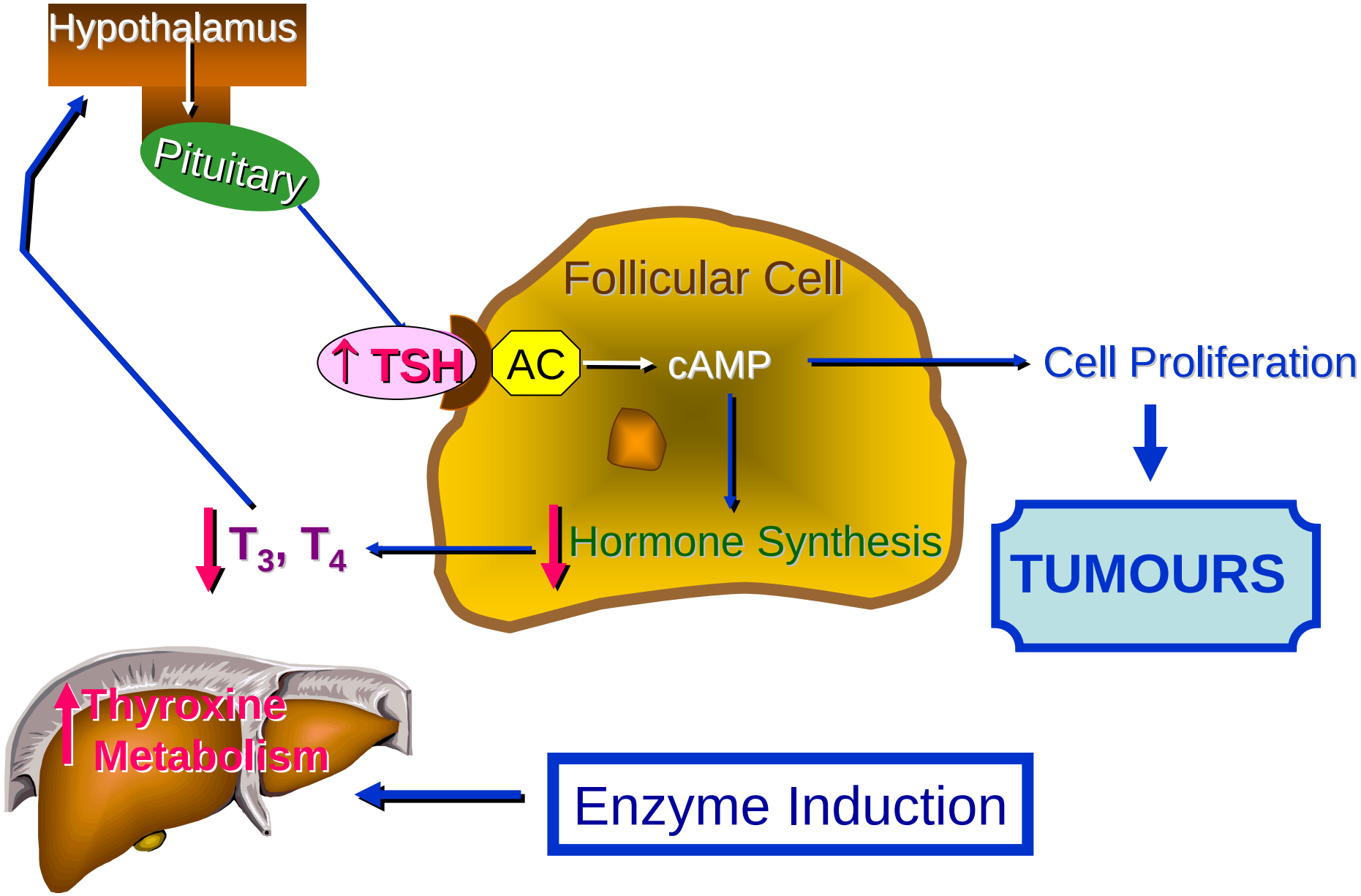
-liver adducts

-changes inT3, T4, TSH inconsistent

-genotoxicity : 1 test of ICH battery positive

Major Objection:
Mechanism of tumorigenesis NOT clarified

Mechanism for Rodent Thyroid Tumorigenesis



Case 1

- **Follow up (mechanistic) Studies Addressing**

-CYP vs T3/T4/TSH

-CYP vs liver adducts

-dose-effect relationships

-comparison to positive control (phenobarbital)

Point Solved ! Could have been anticipated?

EXAMPLES FROM MAAs
Case 2

- **Genotoxicity: Genotoxic Impurity**

-antifungal drug

-for life-threatening condition

- **Genotoxic impurity identifed and required to be lowered/removed**
  - Discussion on “acceptable” levels in case of impossibility to remove
  - Base on benefit/risk for target population

Follow Up:
Guideline on Limits of Genotoxic Impurities

EXAMPLES FROM MAAs
Case 3

Reproductive Toxicity

- Therapy for erectile dysfunction
- Long half life
- Decreased spermatogenesis in dogs
- Altered epithelium of tubules seminiferous
- Severity dose- and time- dependent (low Safety Margin)
- Aspermia after chronic treatment
- Not observed in rodents
- Considered species-specific by the Applicant

Objection Raised:
Mechanism related to MOA? Human relevance?

EXAMPLES FROM MAAs
Case 3 (cont)

Folow up: proposed mechanism

- Increased testicular blood flow
- Increased temperature
- Relevance for man could not be discarded

Information was included in the SPC

Further Developments:

- Long term clinical trial conducted
- Effect Not identified
- SPC updated

EXAMPLES FROM MAAs
Case 4

Cardiovascular Toxicity: Glitazones

- Oral Antidiabetic Drugs
- Agonists PPARɣ
- Reducing factors of Insulin resistance
- Pioglitazone & Rosiglitazone
- NC Concerns identified: CV and Carcinogenesis

Case 4: Pioglitazone

Cardiovascular findings in Dogs and Rats:

-Myocardial hypertrophy not reversible.

-Dose-related mortality appearing related to heart failure/dysfunction.

Safety Margins < 4X
based on animal / human exposure

Follow up NC studies:

Dog and Rats; normoglycaemic vs insulin-resistant

-increased plasma volume correlating with

- •induction of eccentric bi-ventricular cardiac hypertrophy,
- •pericardial and pleural effusion.

-Cardiac hyperthrophy reduced by diuretics

Case 4: Rosiglitazone

Cardiovascular findings in Dogs and Rats:

- **↑ heart rate, cardiac output & stroke volume, with**
  - slight reductions in blood pressure and
  - a significant reduction in total peripheral resistance,

  concomitant with
- **increased heart weight**
  - dependent on treatment duration, Not corr with ECG
  - no safety margin in dogs
- **plasma volume expansion and**
- **↓ erythrocyte parameters;**

Case 4: Rosiglitazone

Proposed Mechanism

- ↑regional blood flow
- ↓total peripheral resistance

↓

Na & H2O retention in the kidney

↓

- ↑ plasma **volume,**
- ↑ preload

↓

Adaptive Cardiac Hypertrophy

Glitazones and Cardiovascular Safety

- Home et al Rosiglitazone evaluated for cardiovascular outcomes--an interim analysis. NEJM 2007;357:28-38.
- 2. Nissen SE, Wolski K.: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. NEJM 2007;356:2457-2471.
- 3. Singh S et al : Long-term risk of cardiovascular events with rosiglitazone: meta-analysis. JAMA. 2007;298:1189-1195.
- 4. Lincoff et al.: Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA.2007;298:1180-1188.
- 5. Lipscombe et al : Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. JAMA. 2007;298:2634-2643.
- 6. Lago et al.: Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials. Lancet. 2007;370:1129-1136.
- 7. Rosen CJ.: The rosiglitazone story--lessons from an FDA Advisory Committee meeting. NEJM 2007;357:844-846.
- 8. Drazen et al.: Rosiglitazone--continued uncertainty about safety. N Engl J Med. 2007;357:63-64.
- 9. Nathan DM.: Rosiglitazone and cardiotoxicity--weighing the evidence. N Engl J Med. 2007;357:64-66.
- 10. Psaty BM, Furberg CD: The record on rosiglitazone and the risk of myocardial infarction. N Engl J Med. 2007;357:67-69.
- 11. Psaty BM, Furberg CD: Rosiglitazone and cardiovascular risk. N Engl J Med. 2007;356:2522-2524

CHMP Conclusions After Re-Assessment

Rosiglitazone and Pioglitazone:

- Benefit/Risk for Type 2 Diabetes Still Positive

- **Rosiglitazone:**
  Warning Included in Prescribing Information

- "Should only be used in patients with ischaemic heart disease, after careful evaluation of each patient's individual risk"

- "The combination with insulin should only be used in exceptional cases and under close supervision".

EXAMPLES FROM SA and PA

Questions Asked

- Study Designs (eg advance therapies, pediatrics)
- Development Programs (eg orphan diseases)
- Need and timing for studies (eg carcinogenicity, reproductive toxicity),
- Studies for Comparability

EXAMPLES FROM SA and PA

Case 5: Selective Receptor Antagonist

- Presence of epitope (n
- Level of homology (ani
- Binding affinity
- Cellular Cascades
- Tissue Distribution of e
- Pharmacological Resp
- Potency

Discussion: Species Relevance

NOAEL in rats: ~18 x human exposure
NEL monkeys: ~44 X human exposure
reprotox planned

	Human	Monkey	Rabbit	Rat
Ki(nM)	0.66	2.5	31.7	78.6

Discussion: # H vs animal Ki
not considered for SR calculations

EXAMPLES FROM SA and PA

Case 6: Authologus Stem Cell Therapy

Nonclinical Program:

- PD
- Safety / Distribution
- Tumorigenicity In immunossupressed mice

- Using the Clinical (human) Product (cells)

SAWP Discussion:

- Use of homologus cells should be considered
- With inclusion of human candidate in (one) treated group
- Studies duration to be adapted to the period of cell persistence

EXAMPLES FROM SA and PA

Case 7: Different Human vs Species Epitope

mAb Targeting One Epitope of Human Immune Cell Type

- different epitope in murine target cells with same function
- Similar cellular cascades driven by the two epitopes in mice and man respectively.

SAWP Discussion:

Strategy Proposed by the Applicant

To uses the mAb against murine epitope in preclinical safety studies to evaluate potential PD-driven safety aspects.

SAWP: Strategy wellcomed and agreed.

Sumarising the "Problems"

- New mechanisms of action

  -to understand the mode of action (MOA)
  -to pick up PD - related toxicological effects
  -to consider/adapt the MOA in the species used

- Human specific molecules (eg proteins, Abs, ...)

  -use homologue molecules in the animal species
  -use animal models of the disease
  -use administration schedules and doses mimicking the human situation

- New Therapy/Technology:(Ped/ Cells/Biotech/Nano)

  -use of adapted approaches

First Advice:

THINK!!

ticking boxes may be confortable but Is NOT

A cost/time effective approach

THANK YOU!