MAA
EU Bladder Issue

Takeda Europe R&D Centre Ltd London

MAA
EU Bladder Issue

- EU R&D have been in a similar situation.
- The Bladder issue was blocking approval.

"Pioglitazone is a male rat urinary carcinogen and the mechanism is not fully clarified"

We succeeded eventually despite a very negative regulatory authority.

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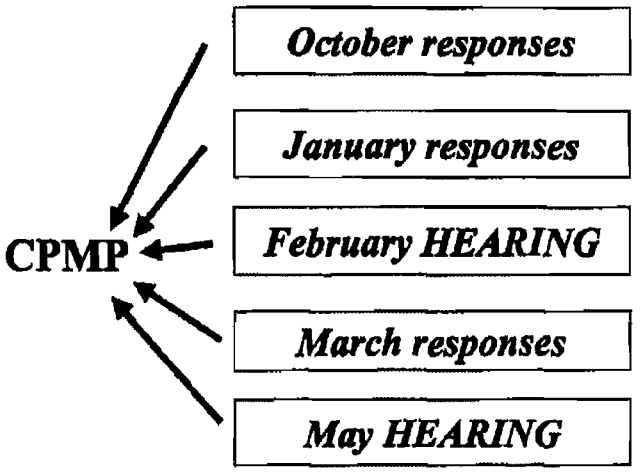
The European Regulatory Authorities

- Doubted Sam Cohen's hypothesis.
- Asked about other possible mechanisms.
  - Including PPAR α hypothesis.
- Pushed for clinical testing.

Multiple discussions with CPMP



CPMP issues -against Sam Cohen hypothesis

- Correlation of tumours and stones is not good.
- Increase in micro crystals is not consistent and not observed at lower dose levels.
- Increase in urine pH is not consistent and not observed at lower dose levels.
- Other mechanisms have not been adequately explored:
  - Local proliferative properties of pioglitazone and metabolites
  - Genotoxicity
  - PPAR α hypothesis

Correlation of tumours and stones is not good.

- 60% is actually quite a good correlation.
- Calculi dissolve.
- Calculi are lost in tissue processing.
- dissolve in fixative

(S18)May hearing

Increase in urine pH is not consistent and not observed at lower dose levels.

- pH generally increased.
- The critical factor is a pH greater than 6.5
- pH is only one of the critical factors:
  - Other factors have not all been identified.

(S18)May hearing

CPMP issues - proposing PPAR α hypothesis

- Piogltazone has shown affinity for other PPAR activation (which has been associated with cell proliferation).

The role of PPAR in tumourigenic responses should also be explored.

Piogltazone has shown affinity for other PPAR activation (which has been associated with cell proliferation).

- Pioglitazone does not produce tumours in tissues where PPAR α and γ are most highly expressed.
- Pioglitazone is not tumourigenic in mice or female rats.
- Pioglitazone is neither a peroxisome proliferator nor a hepatocarcinogen.

Study in this receptor field has greatly advanced since our responses

(S9)Jan resp.p26

CPMP issues -proposing clinical testing -Human risk

- How will the company follow up the potential risk of bladder tumours in patients?
- Risk of colorectal neoplasm?

How will the company follow up the potential risk of bladder tumours in patients?

- Restate the company position (Sam)
- Investigate any malignancies from trials.
- Outcome study data.
- Clinical testing of patients is not helpful.
- Japanese urine clinical study showed nothing.
- A case control study is possible.

(S13)May resp.

Risk of colorectal neoplasm?

- PPAR γ may inhibit the growth of tumours.
- Glitazones only induce tumours in the genetic context of the APC mutation in mice.

(S10)Jan resp.

CPMP issues
-other issues

- Positive result from the PCNA assay.
- Site of contact genotoxicity could be clarified by a COMET assay.
- Genotoxic potential of metabolite MII has not been investigated.
- Interaction of pioglitazone and metabolites with DNA needs further study.
- Structural activity assessment not definative.

Positive result from the PCNA assay.

- No correlation between PCNA index and histology.
- PCNA has limitations.
- BrdU is more sensitive and S phase specific.
  - This test was negative

(S9)Jan resp p24

Site of contact genotoxicity could be clarified by a COMET assay.

- Pioglitazone is not genotoxic.
- COMET assay also positive in apoptosis.
- Assay needs fully validating.

(S9)Jan resp p24

Genotoxic potential of metabolite MII has not been investigated.

- M II is only present in trace amounts in rat urine.
- M II was present in the in vitro mutagenicity studies.

(S6)Oct resp

Interaction of pioglitazone and metabolites with DNA needs further study.

- Not genotoxic.
- Urine from pioglitazone treated rats is not genotoxic.
- Structural activity relationship.
  - Not a rodent carcinogen

Eventual Success: Because of

- **Persistence.**
  - We stuck to Sam Cohen's hypothesis despite many challenges.
- **Argued against clinical testing.**
- **Did not "turn over stones"**
  - eg. Did not undertake database searches.
- **Supported by experts at every opportunity.**