National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Nonclinical aspects in the development of human pharmaceuticals

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Content

1. Goals of safety evaluation
2. Cases from Marketing Authorisation Application
3. Cases from Scientific Advice and Protocol Assistance

Risk mitigation approach

- Goals of Safety Evaluation
  - To identify an initial safe dose and subsequent dose escalation schemes
  - To identify potential target organs for toxicity and for the study of reversibility
  - To identify safety parameters for clinical monitoring
  - To enable benefit-risk assessment at stage of Marketing Authorisation Application

Expectations on Nonclinical Program At the time of filing MAA

- MOST Concerns Should Have Been Addressed and/or Solved/Considered for Risk Management
- Major Nonclinical Problems Should NOT exist!

- **IN THE IDEAL DEVELOPMENT!**

SINCE THE IDEAL DOES NOT EXIST …

Concerns often persist on eg.

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

However, still issues are raised for MAAs

- Poor mechanistic justification
- Poor justification of animal models
- Insufficient Kinetics / Toxicokinetics

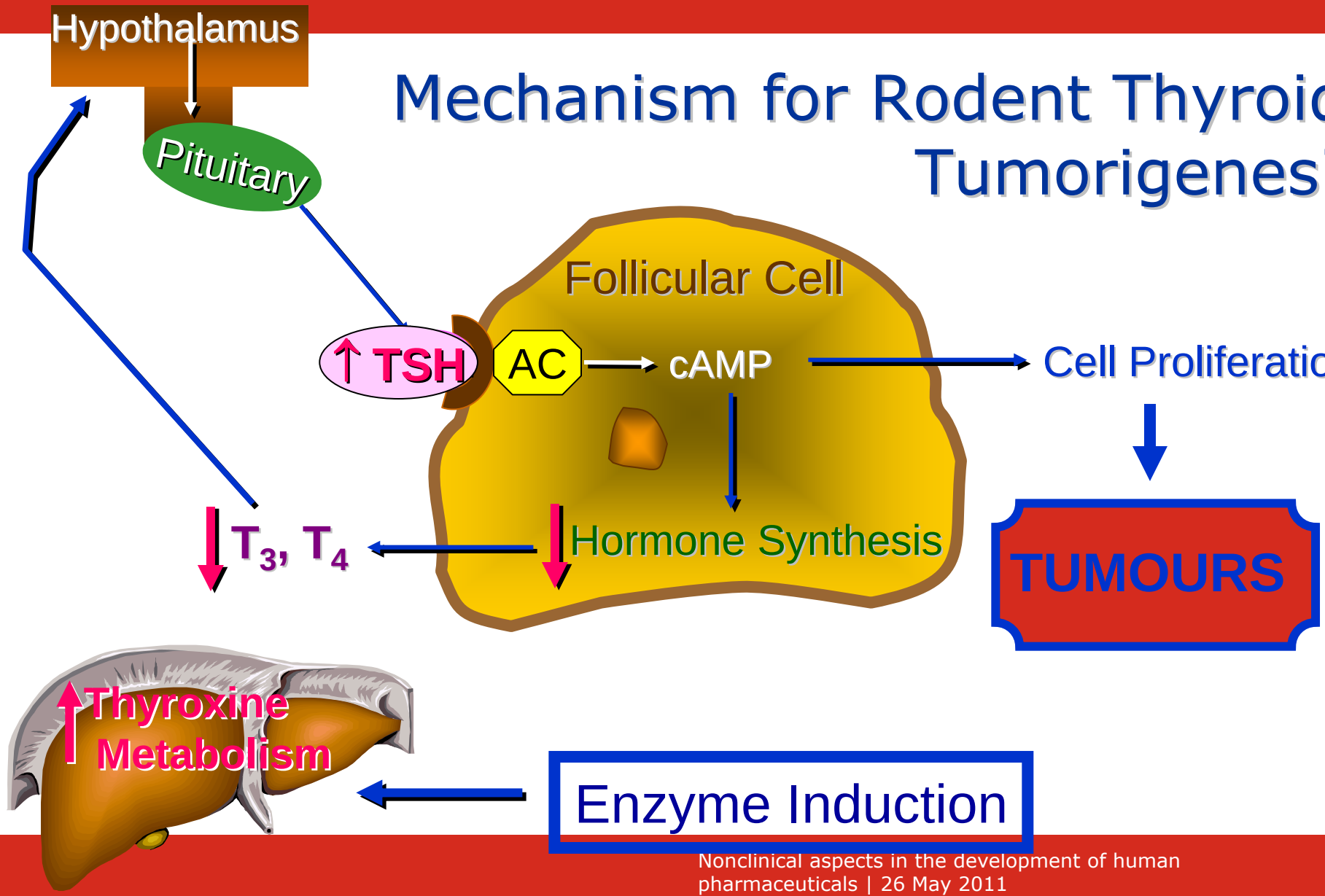
EXAMPLES FROM MAAs
Case 1, small molecule

- Carcinogenicity 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?

B. Silva Lima, J.W. van der Laan. *Regul.Toxicol.Pharmacol*. 2000; 32: 135-143

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

- **Exetanide (Byetta) /Liraglutide (Victoza)**
  - Exetanide benign thyroid C-cell adenomas in female rats, high dose only. No carcinomas observed.
  - Liraglutide C-cell tumours observed in mice and rats at therapeutic levels (in rats).
  - Other tumours (uterus leioma, leisarcoma, skin sarcomas) in mice. These tumours not a risk for humans.

Major Objection:
Mechanistic explanation has to given by the company

EXAMPLES FROM MAAs
Case 3

- **Liraglutide (Victoza)**
  - GLP-receptors in C-cell of all species, in rats with higher density per cell than in humans
  - C-cells less abundant in human thyroid as compared with rodent thyroid.
  - In rat C-cell liraglutide induced cAMP and calcitonin secretion, whereas in human cell line the response was marginal
  - GLP-1 expression (measured by mRNA) is much lower in human cells compard with rat C-cells, but not completely absent.

Rodents are highly sensitive to GLP-1 mediated-mechanism. Relevance for humans is low but cannot be completely excluded

General Principle on Guidelines

- Guidelines are purposed to help development of pharmaceuticals
- Guidelines are not written to stop development.
- If there are good scientific reasons not to follow a guideline, do it, and justify it explicitly
- In case of doubt ask scientific advice

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/Biosimilarity

EXAMPLES FROM SAs

Case 4

Monoclonal antibody

- Therapy for Type 1 Diabetes Mellitus
- Chimeric (humanized/rat)
- Species specific nonhuman primate
- No surrogate available

Discussion items

- Need for Juvenile studies
- Developmental studies

EXAMPLES FROM SAs

Case 4

Juvenile studies

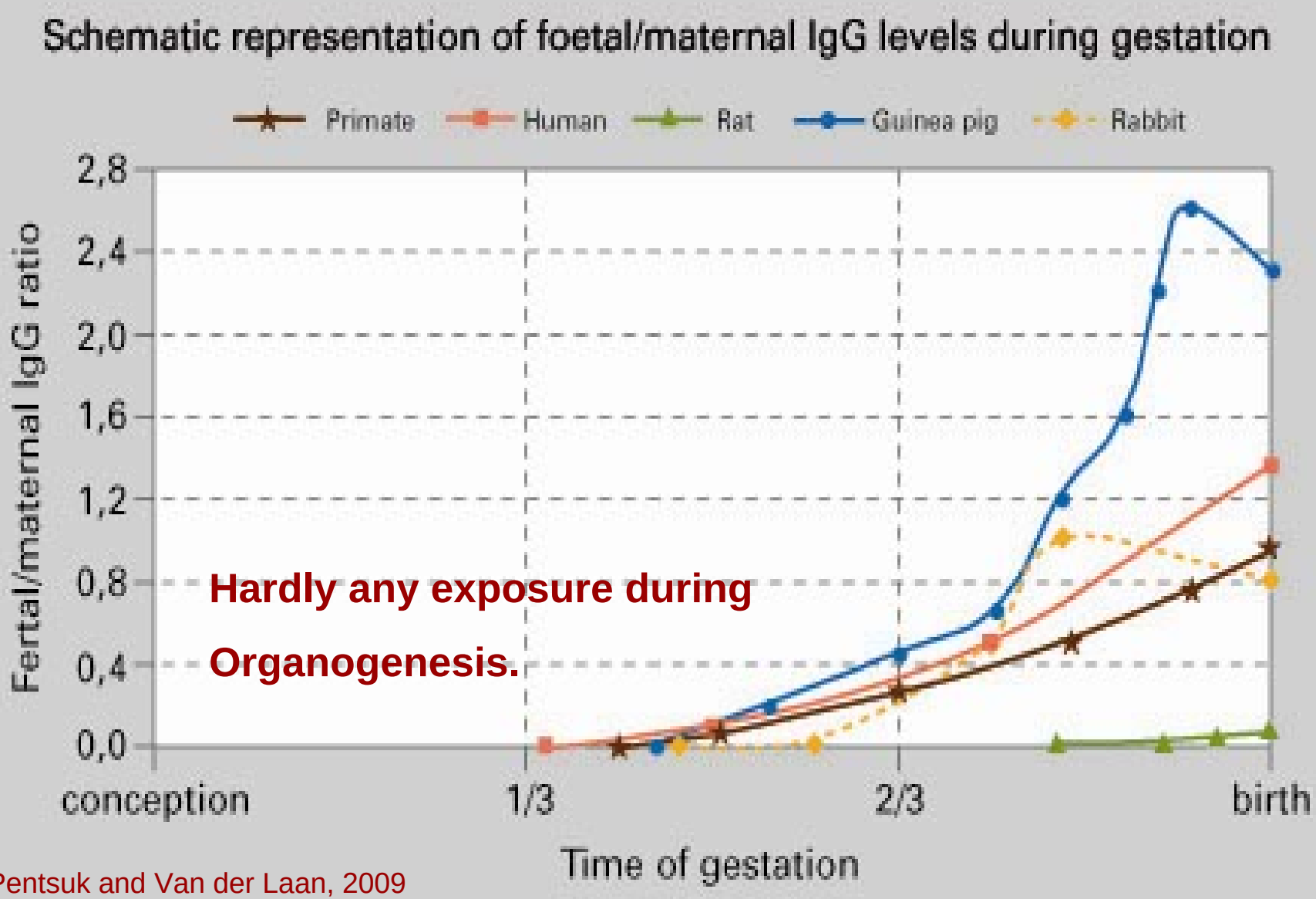
Type 1 DM may start before 5 yrs.
Immune function matures during 0-12 yrs

Developmental Immunotoxicity studies may be needed

Developmental studies

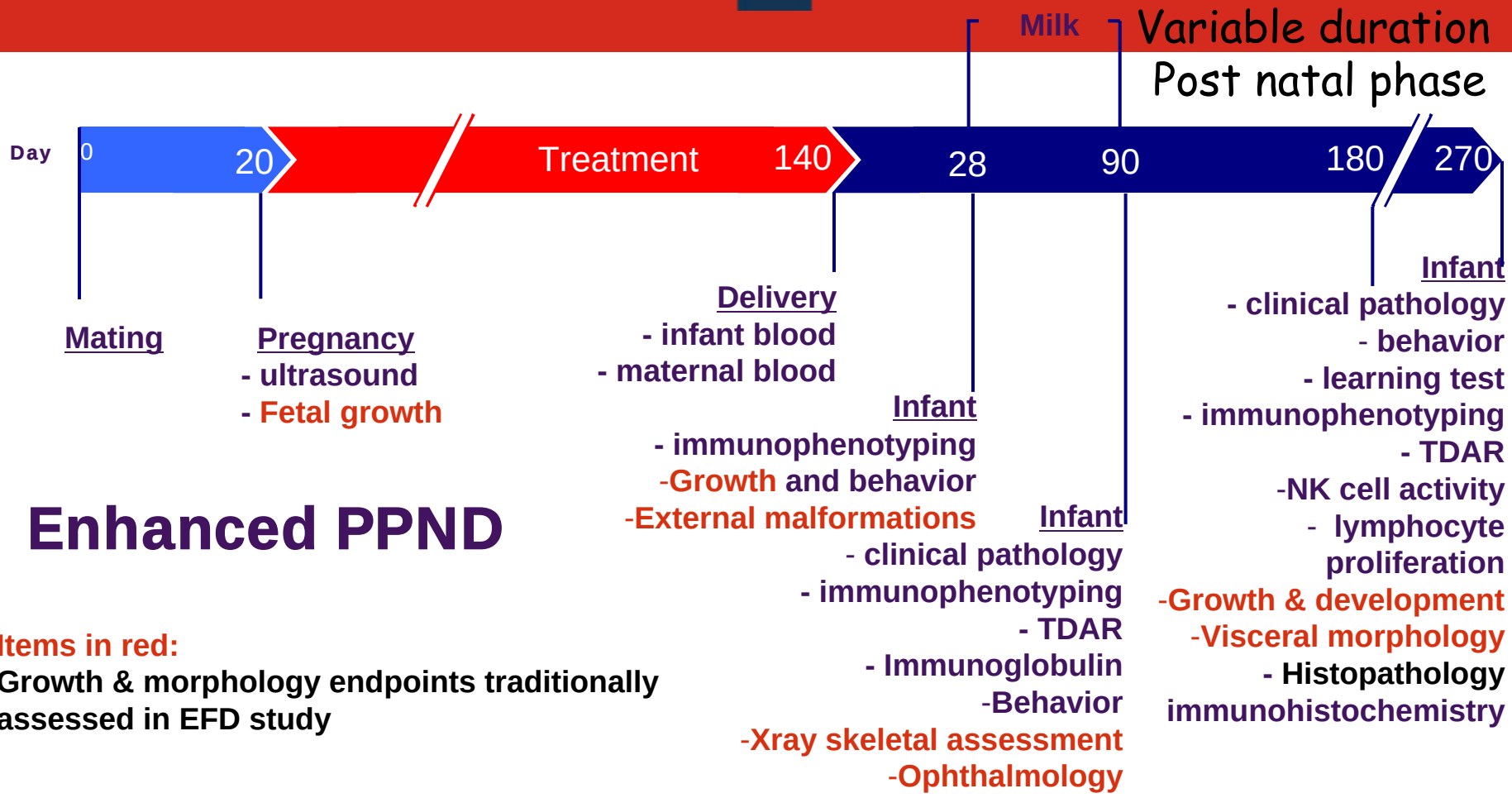
Type 1 DM may include young girls at sexually maturing age.
IgG antibody will be transfered over the placenta

Is there any interference with immune maturation during 3rd trimester?



Pentsuk and Van der Laan, 2009

Rodents: IgG transfer up to maternal level during lactation



Enhanced PPND

Items in red:
Growth & morphology endpoints traditionally assessed in EFD study

Postnatal phase duration & endpoints designed to address specific mAb concerns eg ontogeny of immune system, CNS development etc

From Stewart, 2009

EXAMPLES FROM MAAs
Case 4 (cont)

Important risks

- Interference with growth during maturation
- Interference with immune system development after birth

Further Developments:

- **ePPND study in cynomolgus monkeys?**
- **long-term postnatal monitoring?**

Examples from Scientific Advice

Case 5: Biosimilar Monoclonal Antibody

Monoclonal antibodies run out of patent and dossier protection

- amino acid sequence identical
- glycosylation might be different
  (based upon other cell line for production)
- receptor binding and function is similar in target cells
- product is specific for humans and non-human primates

Are studies in non-human primates needed to support marketing authorization application?

Examples from Scientific Advice

Case 5: Biosimilar Monoclonal Antibody

Monoclonal antibodies are specific pharmacological molecules

- Toxicity is in most cases exaggerated pharmacology
- Other safety aspects can be covered by in vitro studies
- NHP's not adequate for Cytokine Release Syndrome
- Immunogenicity not predictable for human immunogenicity
- IgG character responsible for pharmacokinetic properties
- in vitro data more sensitive in detecting differences between biosimilar product and innovator.

Studies in non-human primates have in general no added value in safety testing of biosimilar MoAb's

Examples from SA and PA

Case 6: Autologous Stem Cell Therapy

e.g. treatment of corneal lesions

Nonclinical Program:

- PD
- Safety / Distribution
- Tumorigenicity In immunossupressed mice
- Using the Clinical (human) Product (cells)

EXAMPLES FROM SA and PA

Case 6: Autologous Stem Cell Therapy

Nonclinical Program:

- Pharmacodynamics – proof-of-concept

SAWP Discussion:

- Homologus cells in animal models commonly used
- In vitro data with human cell product generally sufficient

Comparison with existing cell therapies is possible, if relevancy can be shown.

EXAMPLES FROM SA and PA

Case 6: Autologous Stem Cell Therapy

Nonclinical Program:

- Distribution: issues - Detection of cells
- Cellular antigens often species specific

SAWP Discussion:

Use of homologus cells should be considered in animal models

- Detection with luciferase-gene incorporation
- male cells in female animals-detection with qPCR
- immunocompromised animals-detection with PCR

Case 6: Autologous Stem Cell Therapy

Tumorigenic risk

- Karyotypic analysis no guarantee of absence of transformation.
- altered karyotype may not be the result from transformation, but could also be a signal of senescence.
- altered karyotypes are common among tumour cells.

Therefore *in vitro* karyotypic analysis can still be considered to provide some reassurance against transformation.

Evaluation growth factor dependence an alternative approach?

- this should be validated as well,
- In particular the positive control (growth independent) cell line and the composition of the culture medium may need some research.

Case 6: Autologous Stem Cell Therapy

Tumorigenic risk

- Additional studies
  - Soft agar colony formation:
  - Cmyc (oncogen) expression,
  - Telomerase activity
  - Status of the cell with respect to differentiation (terminal differentiated are unlikely to be tumorigenic)

Last resort:

..

- Tumourigenicity in immune-deficient animals
  Although in EP, validity not proven (feel good study)

Conclusions

- New mechanisms of action
  - -to understand the mode of action (MOA)
  - -to pick up PD - related toxicological effects
- 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 might be comfortable but
Is NOT cost/time effective.
Scientific Justification is more important