EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

BOS1 Regulatory Discussant

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2. How M&S is currently used in industry?

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-Thanks to the industry and academy we're going to this direction

-Mainly used in predicting the dose for FIM + other similar "simple one hit" studies

- Receptor binding characteristics of chemical drugs, monoclonal antibodies, iRNAs *etc*
- Population based PK modelling

- **Sanda Visser's example**: PK/PD modelling of well conserved hormone regulation (T4/T3) – prediction of hormone levels using surrogate end point thyreoperoxidase (TPO) *in vitro*

-Has the model been used in "pivotal" studies aimed for MAA?

-How to incorporate these data to predict thyroid responses in man without any animal studies

-Have you refined the model based on human data with additional chemicals?

3. Is there room for improvements?

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- Could the test system forecast true thyreotoxic/goitregenic substances?
- Were any goitregenic substances tested?
  - Were +/-ive controls included into the tests?
- How many compounds you have tested in the platform, were the results in line?
- Does the model take into consideration both active and passive transport into different compartments?
- Have pH changes in different compartments been taken into consideration when establishing the model?
- Have the protocol - as used here - been published in the literature or any other forum under open debate?
- Are you using open share or commercial programmes? Based on your experience is there any difference between the platforms?
- “Anonymous structural characteristics” – target/non-target toxicity?
- Is there any in vitro/in vivo reference data base (gold standard) established against which one could compare own data?

Topic 1 Personal general comments

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- How M&S is currently used in industry?
  - Less used in questions stated to CHMP/SAWP/SWP level
  - Can industry/Academy answer to this question after today's workshop – has the profile changed during last 5 years?
- What is the regulatory experience/acceptance of M&S?
  - At early phase, only a few regulators are familiar with M&S. Use when ever possible and try to convince other stakeholders.
- Identify Gaps and Room for improvement
  - Nonclinical studies: A lot need to be done, start with a simple questions – liver, kidney… toxicity. Define toxic endpoint(s), make a study strategy proposal according to relevant guidance/guidelines and go for it

Topic 1 Personal general comments…

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•Is there room for improvement in the **nonclinical evaluation** of new drugs? – Definitely, continuous learning process!

- In vitro/in vivo
- New tools, omics, translational pharmaco/toxicology, *in silico* (M&S),
- *in cerebro* – scientific rationale!

•How regulators and industry envisage sharing the results of M&S at this sage of development?

- Open dialogue is needed - who will teach regulators?

•What are the standards expected for use and reporting if M&S is used as a basis to justify deviation from the preclinical regulatory requirements?

- Scientific rationale should be the driving force
- Nobody knows at this early stage of modelling & simulation

Topic 1 Personal general comments…

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•**Sharing data**, to establish an open “clean database”– a key issue for any successful development.

- “Anonymous structural characteristics/descriptor-based database” – target/non-target toxicity?
- EMA – collection of all data on drugs on markets and those that failed