Case Studies: Use of Alternative Methods for Registration.

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Setting the stage

- Sources of information:
  - Industry through professional contact
    - Cosmetic, Pharmaceutical, Chemical, Food and Consumer Product industry
  - *In Vitro* Testing Industrial Platform
    - About 40 companies active in the area of animal-free testing and assessment
      - About 30 are SMEs.
- Overall, the application of animal-free approaches for testing and assessment of substances and products is slow.
  - Innovation that benefits the few

Several explanations for low application

- Lack of specific *in-house* competence
  - Identification of suitable animal-free methods
  - Combination of methods into suitable testing or assessment strategies
  - Evaluation and reporting of data generated through novel methods
- Uncertainty about costs and regulatory acceptance
  - Costs related to training, and method evaluation and adaptation
  - Battery of animal-free test methods often more expensive than existing animal-based test methods
- Lack of practical information

Case Study 1 – Consumer Products: Registration based on historical data

- Extensive analysis of data collected over several decades
  - Human clinical data
  - Animal data originating from several animal-based test methods
  - *In vitro* and *in silico* data
  - Expert judgement
- Classification of the products based on 'hazard' profiles
  - Setting of 'relative' safety limits
- Important pillar in safety assessment dossiers.

Case Study 2 – Chemical (1): When test guidelines stop innovation

- Product:
  - A biomaterial with a variety of applications
- Animal testing:
  - Safety-cleared for every intended application by every animal-based test guideline method used
    - Mice, rats, rabbits, dogs
      - Acute toxicity, sensitization, carcinogenesis, inflammation, …
- Exposure to humans:
  - Severe adverse effects in at least two applications .

Case Study 2 – Chemical (2): When test guidelines stop innovation

- Animal-free testing:
  - Based on the intended application, an *in vitro* non-test guideline test strategy was composed.
    - Focussing on inflammation
      - Animal models for inflammation have a low productivity for human inflammation
  - The acquired mechanistic understanding guided production process improvement.
    - *In vitro* biological profiles of the 'improved product' and approved competitive products became identical.
- Dossier:
  - Animal testing is still required, but what will this investment at all provide confidence in the safety of the product?

Case Study 3 – Chemical (1): When testing becomes redundant

- Product:
  - Chemical mixture.
  - Analytical methods provided qualitative and quantitative information about the chemical composition.
    - Several well known and characterised carcinogens
  - Concentrating to reach effect levels causes precipitation
    - Concentrate not representative for the product
- Animal testing:
  - The total carcinogen concentration is several orders of magnitude below concentrations reported to trigger adverse effects in currently used animal-based test guidelines.

Case Study 3 – Chemical (2): When testing becomes redundant

- Animal-free testing:
  - The total carcinogen concentration is several orders of magnitude below concentrations reported to trigger effects in currently recommended *in vitro* testing strategy for genotoxicity.
- Human exposure during application:
  - Estimations of the exposure levels for humans reveal carcinogen exposure levels that are 200-700x below accepted NOAELs in humans.
- Dossier:
  - Testing is still required by the authorities.
- Marketing is currently put on stand-by.

Conclusion

- The information provided in dossiers should contain 'sufficient confidence' about the toxicity (or lack there off) of a substance or product.
- Building 'sufficient confidence' should be science-driven, even when the science is provided by adapted test guideline or well-documented non-test guideline methods.
- Innovation cannot flourish unless it is applied at all levels.