Environmental Risk Assessment

Catriona Cooke

Director, Ecotoxicology and Regulatory Services

Smithers Viscient

www.smithersviscient.com

catriona.cooke@smithers.com

Environmental Risk Assessment

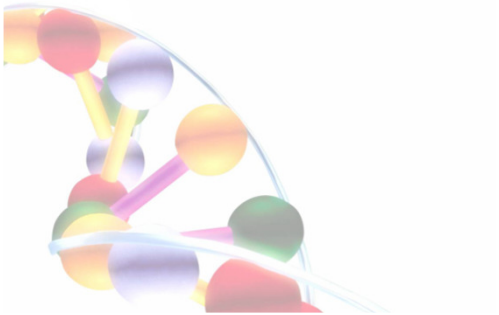
In this presentation we will cover

- Legislative background – EU and US
- Risk assessment framework
  - Estimation of exposure
  - Trigger levels
  - Testing requirements
  - Risk characterisation
  - Exceptional circumstances
  - Refinement
  - Expert report
- Post-submission

Legislative background - EU

- Directive 2001/83/EC
  - Article 8(3) (as amended)

"The application shall be accompanied by the following particulars and documents, submitted…
…Evaluation of the potential environmental risks posed by the medicinal product. This impact shall be assessed and, on a case-by-case basis, specific arrangements to limit it shall be envisaged."

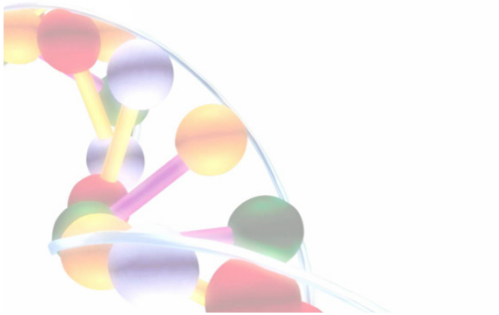


Legislative background - EU

- European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP)

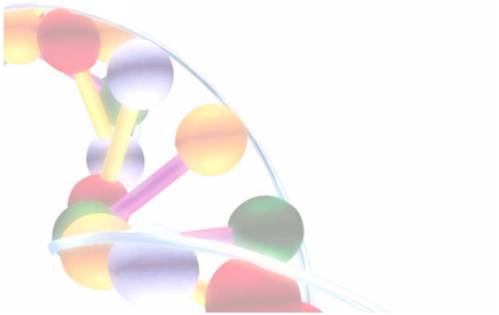
  - 1st June 2006: Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use

  - 17th March 2011: Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'



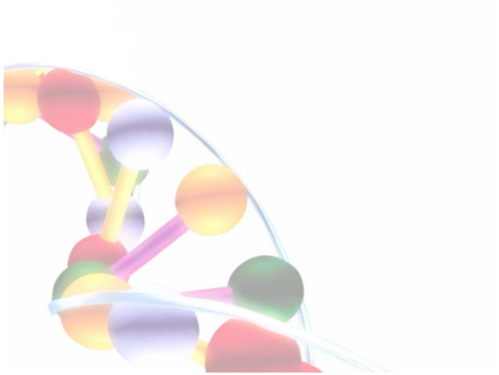
Legislative background - US

- National Environmental Policy Act of 1969 (NEPA)
  - All Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses
  - The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impacts of approving drug and biologics applications as an integral part of its regulatory process



Legislative background - US

- Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (US FDA)
  - July 1998: Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications



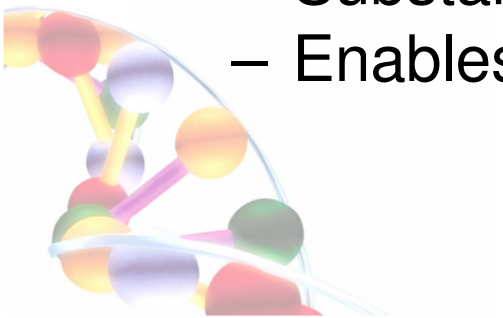
Risk Assessment Framework

Exposure

- Opportunity for harm to occur, requires contact between organism & chemical
  Controlled by:
  - Release of chemical to the environment
  - Fate processes (transport & degradation)
- Measure = concentration present in environment

Hazard

- Potential to cause harm (effects)
- Substance-specific
- Enables risk characterisation (MSDS, C&L)



RISK = *f*{exposure, hazard}

Risk Assessment Framework

Estimation of Exposure

- EU = Predicted Environmental Concentration (PEC)
  - Based on maximum daily dose
  - Assumptions:
    - No metabolism in patients
    - No retention or biodegradation in STP
    - No degradation in the environment

$$PEC_{sw} = \frac{Dose_{(ai)} \times F_{pen}}{WW\ (inhab) \times Dilution}$$

  - Trigger level for testing ≥ 0.01 µg/L

Risk Assessment Framework

Estimation of Exposure

- US = Expected Introduction Concentration (EIC)
  - Based on annual tonnage produced
  - Assumptions:
    - No metabolism in patients
    - All drug products produced in a year are used and enter the publicly owned treatment works (POTW) system
    - Drug product proportionate to population and waste water generated

$$\text{EIC-Aquatic} = \text{kg/year} \times \text{WW(L/d)} \times 1/365 \times 10^9 \ (\mu\text{g to kg})$$

  - Trigger level for testing ≥ 1 µg/L

Risk Assessment Framework

Estimation of Exposure

- Predicted exposure is below trigger level:

EU

  - Phase I PEC report

US

  - Categorical exclusion

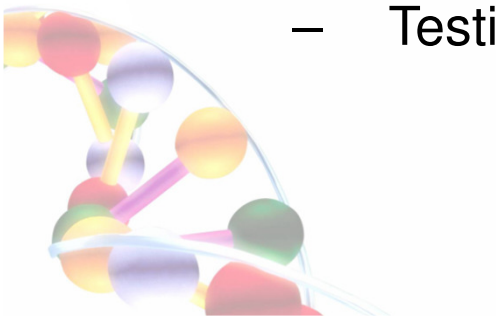
(unless exceptional circumstances)

- Predicted exposure is above trigger level:
  - Environmental fate and effects testing are required
  - Formalised environmental (risk) assessment

Risk Assessment Framework

Other considerations (exceptional circumstances)

- Both approaches require consideration of potential endocrine disruption (ED)
  - Review of existing mammalian toxicology data
  - Analysis of any public domain information
  - Testing from screening to partial/full life cycle may be required
- PBT (Persistent, Bioaccumulative, Toxic) testing can be triggered, even when estimated exposure is below the trigger value
  - EU = log K_{OW} > 4.5
  - Testing conducted in a stepwise manner



Risk Assessment Framework

Testing Requirements

- Physicochemical properties
  - Solubility
  - Octanol/water partition coefficient
- Environmental processes
  - Biodegradation
  - Adsorption to soil/sludge
  - Photolysis/hydrolysis
- Effects on organisms
  - Microorganisms
  - Aquatic species (3 trophic levels)
  - Terrestrial species

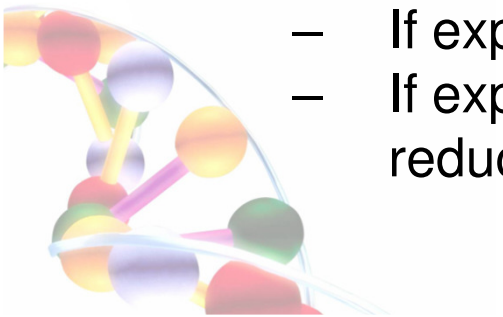
Risk Assessment Framework

Risk Characterisation

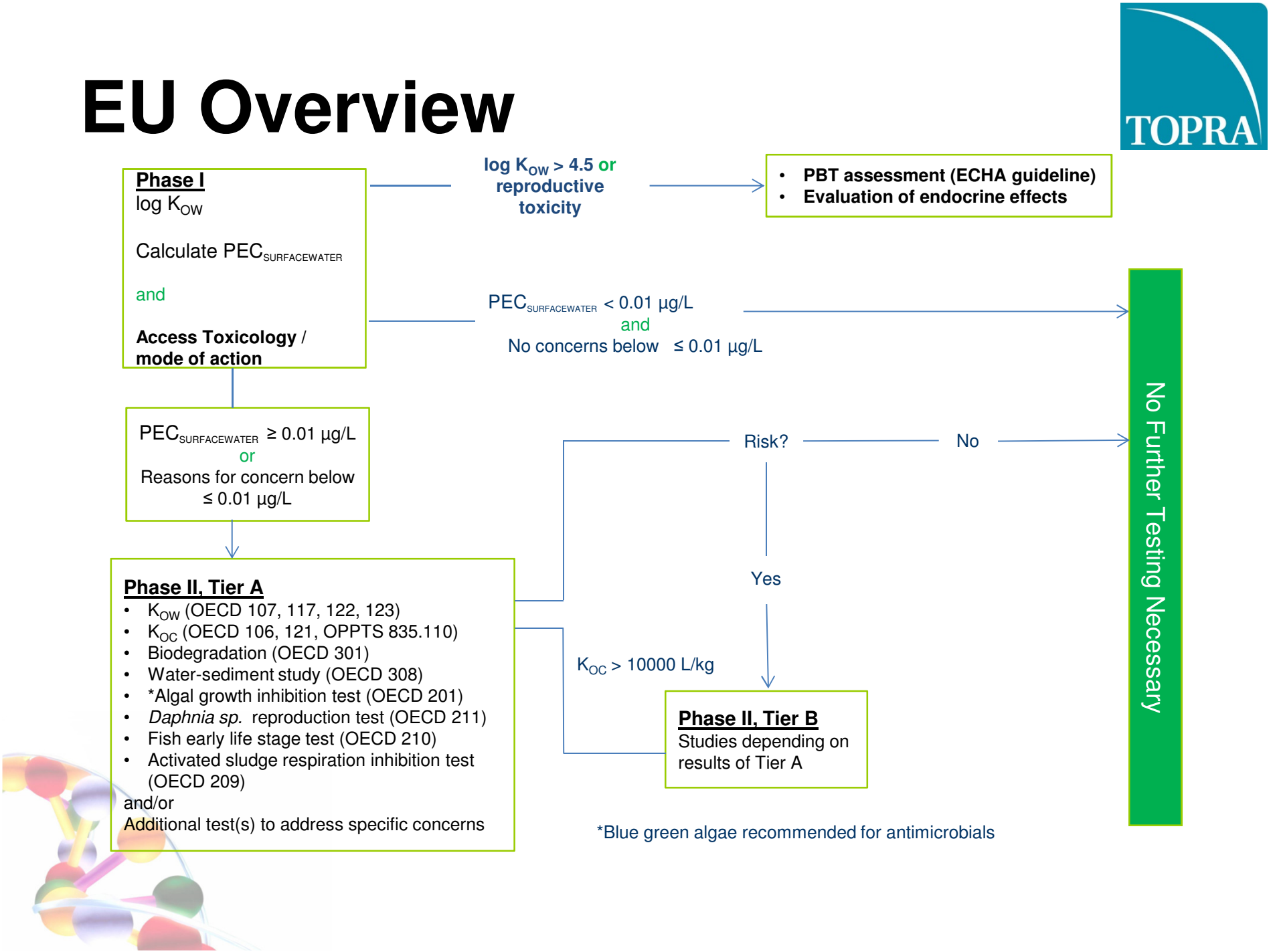
RISK = f\{exposure, hazard\}

- Effects studies determine Predicted No Effect Concentration (EU) or Lethal/Effective Concentration (LC_{50}/EC_{50}) (US)

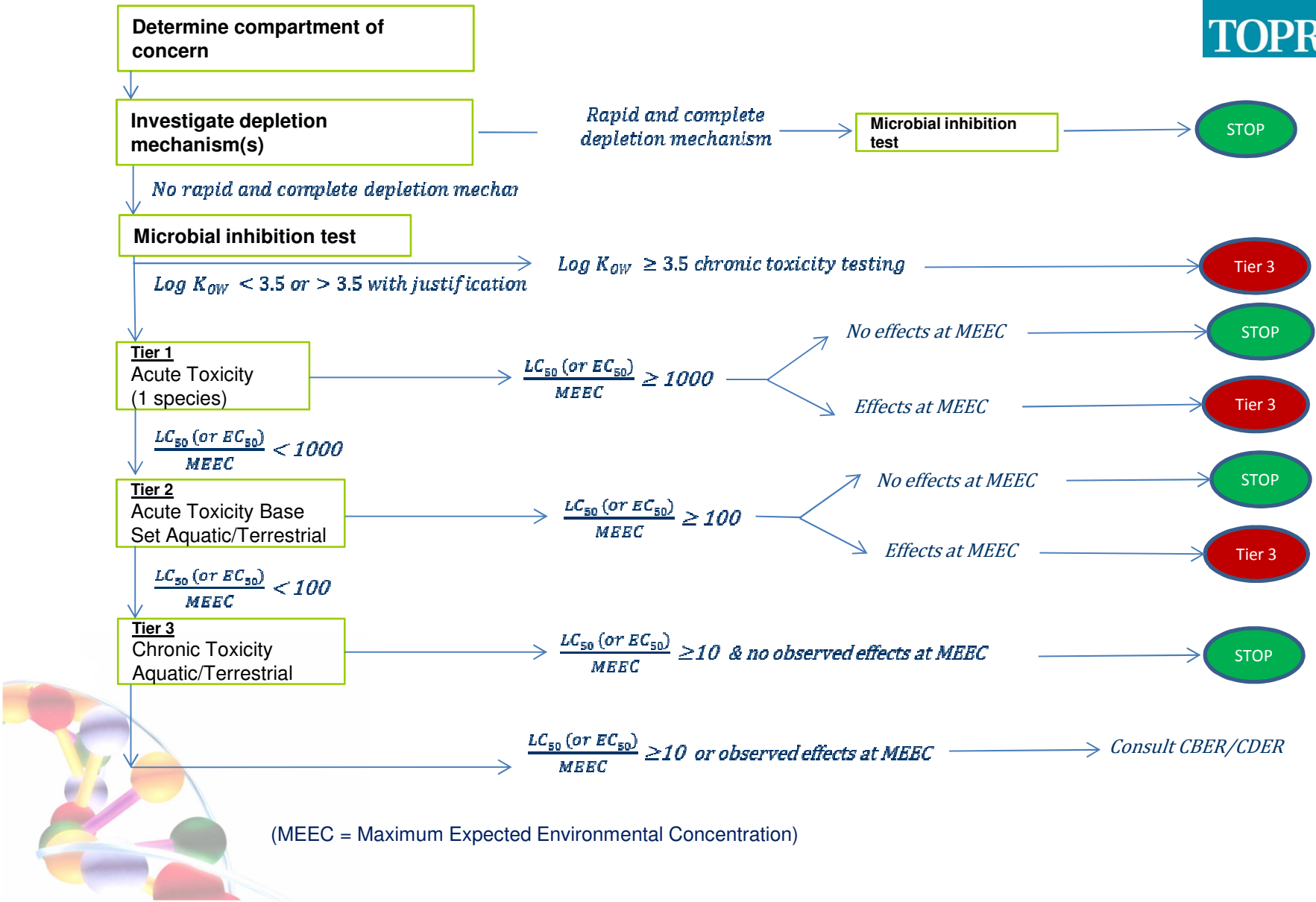
- Determine exposure:hazard ratio in relevant compartments
  - If exposure < hazard, unlikely to be a risk
  - If exposure > hazard, more testing required and/or look to reduce PEC



EU Overview


Phase I
log K_{OW}
Calculate $PEC_{SURFACEWATER}$
and
Access Toxicology / mode of action
log K_{OW} > 4.5 or reproductive toxicity
• PBT assessment (ECHA guideline)
• Evaluation of endocrine effects
$PEC_{SURFACEWATER}$ < 0.01 µg/L
and
No concerns below ≤ 0.01 µg/L
$PEC_{SURFACEWATER}$ ≥ 0.01 µg/L
or
Reasons for concern below ≤ 0.01 µg/L
Risk?
No
No Further Testing Necessary
Yes
Phase II, Tier A
• K_{OW} (OECD 107, 117, 122, 123)
• K_{OC} (OECD 106, 121, OPPTS 835.110)
• Biodegradation (OECD 301)
• Water-sediment study (OECD 308)
• *Algal growth inhibition test (OECD 201)
• *Daphnia sp.* reproduction test (OECD 211)
• Fish early life stage test (OECD 210)
• Activated sludge respiration inhibition test (OECD 209)
and/or
Additional test(s) to address specific concerns
K_{OC} > 10000 L/kg
Phase II, Tier B
Studies depending on results of Tier A
*Blue green algae recommended for antimicrobials

US Overview

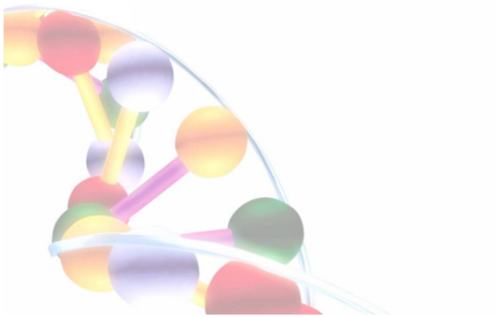


(MEEC = Maximum Expected Environmental Concentration)

Risk Assessment Framework

Refinement

- Metabolism and excretion
- Fpen (EU)
  - Market share
  - Prevalence of indication
  - Treatment regime
- Mitigation measures



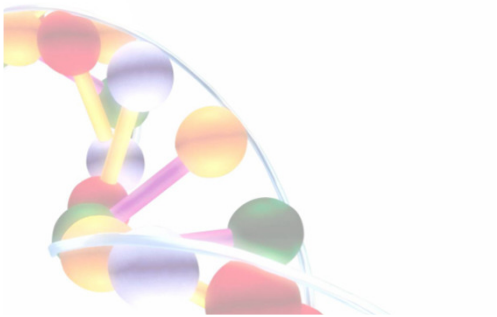
Risk Assessment Framework

Expert Report

- Formalised risk assessment
  - Identity of drug substance
  - Proposed application(s)
  - Proposed dose / tonnage produced
  - Summary of physicochemical properties
  - Results of fate and effects testing
  - Risk characterisation
  - Recommendations for further testing/investigation (if required)
  - Overall conclusion
- Submit to EU EMA / US FDA

Post-submission

- Evaluation by regulatory agency
- Formalised comments
  - Validity of studies submitted
  - Recommendations for additional testing
  - General clarification
- Provision of responses
- Acceptance of risk assessment



Summary

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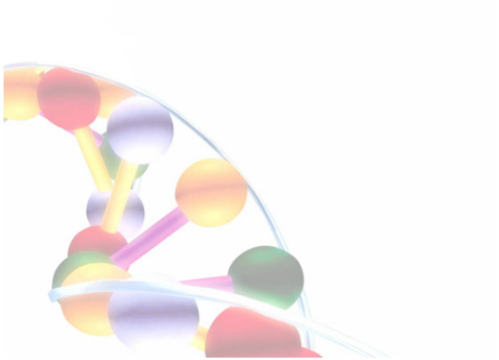
  - Exposure
  - Hazard
  - Risk Characterisation
  - Refinement
- Post-submission

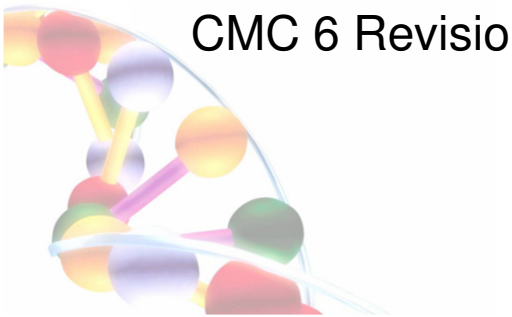


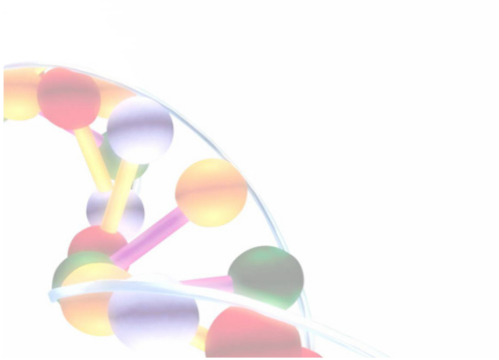
Summary of recommended references

- Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency. **Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use**. (Doc.Ref.EMEA/CHMP/SWP/4447/00 corr 1) 01 June 2006

- Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency. **Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use'**. (Doc. Ref. EMA/CHMP/SWP/44609/2010) 17 March 2011

- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER). **Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications**. CMC 6 Revision 1, July 1998





QUESTIONS