Federal Environment Agency, Dessau-Roßlau

Experiences with environmental risk assessment in the authorization procedure of Veterinary Medicinal Products

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What this talk is about …

- Legal background
- Environmental risk assessmemnt
- Experiences with ERA of VMPs
- Authorisation procedure & Eco-Pharmacovigilance
- Summary

Administration in Germany

Federal Ministry for the Environment, Nature Conservation and Nuclear Safety

Federal Ministry of Food, Agriculture and Consumer Protection

ERA of VMPs

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UBA

Federal Office of Consumer Protection and Food Safety

BVL

Administration in Germany

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Applicant

Opinion of
Federal Office of Consumer Protection and Food Safety (BVL)
is in **consent** with
Federal Environment Agency (UBA)

Dossier

BVL

ERA

UBA

UBA assessment

UBA assessment

Assessment on other parts of the dossier

DE Opinion on Quality, Clinical part, Non-Clinical part, ERA etc.

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Legal background

Legal background

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1992 Issue of environmental safety of pharmaceuticals first introduced into European drug regulation (92/18/EC amending 81/852/EEC)

1993 Council Regulation (EEC) No 2309/93 on centralised authorization procedure and establishment of EMA

2001 Consolidation of pharmaceutical legislation (2001/82/EC)

2004 EU Pharma review: Environmental Risks part of the benefit/risk analysis (2004/28/EC, amending 2001/82/EC)

- An ERA is necessary for all types of application: new products, generic products, bibliographic applications, hybrid applications, type II variations and extensions.

Legal background

(Directive 2001/82/EC as amended in 2004)

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- Environment – part of the **risk definition** [§ 1(19)]
- MA shall contain an indication of potential risks that the VMP might pose to the environment and tests for assessing the potential risks [§12 (3); Annex I]
- Environment: part of the **benefit-risk analysis** [§ 1(20)]
- Authorization may be linked with **risk mitigation measures** to reduce identified risk for the environment
- Obligation to report on environmental risks within **post-marketing surveillance**

Technical guidelines for ERA

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- VICH-guidelines describe the phased approach of an ERA.
- Supporting document of European Medicines Agency (EMA) focuses mainly on exposure assessment.

1992

2007 Technical Guideline in support of VICH guidelines (EMEA/CVMP/ERA/418282/2005)

2005 VICH Phase II (CVMP/VICH/790/03)

2000 VICH Phase I (CVMP/VICH/592/98)

1998 EMEA Guidance document (EMEA/CVMP/055/96)

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Environmental risk assessment

according to EMA-Guidelines

Guideline on ERA for VMPs

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Guideline (EMEA/CVMP/ERA/418282/2005-Rev.1) contains two approaches

RISK Assessment: Exposure based: PEC/PNEC approach

Predicted environmental concentration / Predicted no effect concentration

->refinement, risk mitigation measures or benefit-risk-analysis

HAZARD Assessment: based on intrinsic properties: PBT
(Persistence, Bioakkumulation, Toxicity)

-> no risk mitigation measures possible - benefit-risk-analysis?

Environmental Risk Assessment

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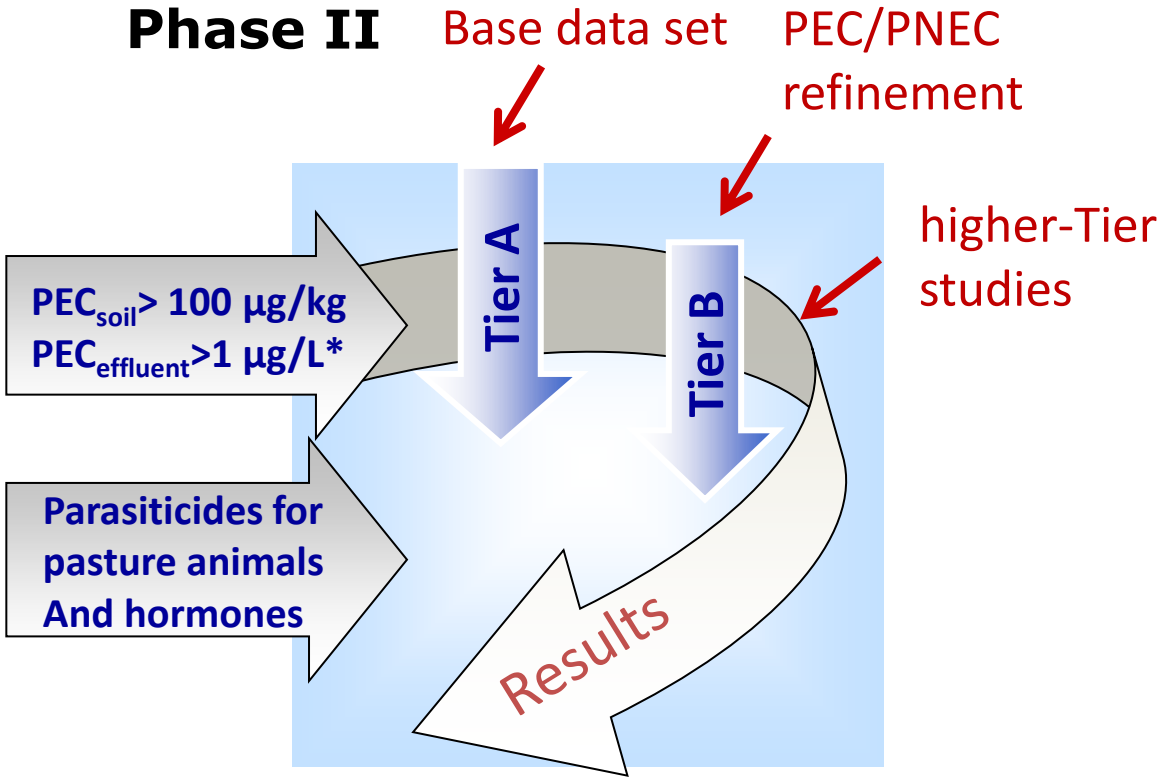
Phase I

- relevance?
- exposure assessment
- Comparison with trigger values to identify those products, for which Phase II assessment is required
- exemption: parasiticides

No relevant exposure

-> no further assessment

Phase II



- no risk
- benefit-risk-analysis
- risk mitigation measures

Environmental Risk Assessment

Risk characterization for each compartment
(soil, pasture, surface water, ground water, sediment)



$$RQ = PEC_{refined} / PNEC$$



RQ <1 no risk → agreement on the authorisation of the VMP

RQ ≥1 environmental risk → risk mitigation measures or no agreement on the authorisation of the VMP -> benefit-risk – analysis (CVMP)

photos: Ines Rönnefahrt

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Experiences with

Environmental risk assessment

UBA experiences with ERA

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- UBA is involved in authorization procedure of VMPs since (1998) 2005. About 120 active substances assessed so far (but not for all substances complete data sets available).

- Pharmaceutical substances with high environmental concern:
  Parasiticides: harmful effects on non target organisms e.g. dung insects and other insects & organisms (protozoa, worms etc.) in soil and surface water

  Antimicrobials: harmful effects on algae and plants, accumulation in soil, development of antimicrobial resistance

  Hormones: effects on the hormonal system of fish, mollusks, invertebrates and birds. Effects on fish e.g. impaired reproduction, changed behavior, intersex

  Substances with P-B-T or vP-vB characteristics: environmental risk is unpredictable

UBA experiences with ERA

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- Effect assessment within the EMA guidances is effective for most drug classes, but:

  - Effect assessment of antimicrobials?
  - Tailored risk assessment for hormons?
  - Effects of life-long exposure to very low levels of pharma-ceuticals?
    → No methods are available to evaluate such effects!

Challenges for future research and regulation !

UBA experiences with ERA

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- Existing (‚old') substances:
  (active substances of VMPs which were approved before the requirement for an ERA was introduced into the legislation)
  → often no full data sets on env. fate & effects available

- Duplication of data on pharm. substances due to different applicants (various VMPs with identical active substance)

- Criteria on benefit-risk assessment regarding harmful effects on the environment ? No VMP was refused so far based on a negative benefit-(environmental) risk analysis!

- Only few examples of risk mitigation measures on a product level are available. Restrictions on use of VMPs are often not feasible. → Risk mitigation measures will not effectively reduce the environmental pollution !

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Authorisation procedure

&

Eco-Pharmacovigilance

Environmental risk assessment in the authorization procedere

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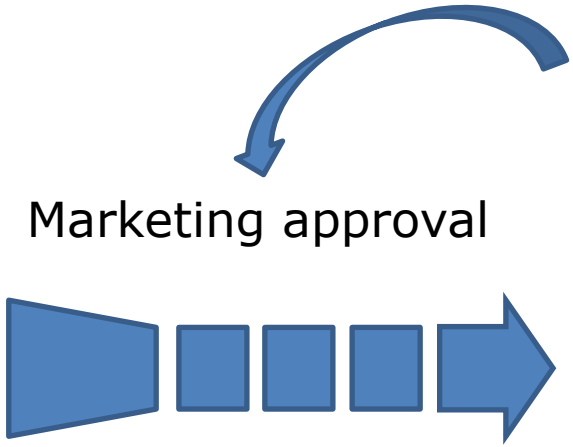
Pre market surveillance

administrative information and scientific documentation



Post market surveillance (pharmakovigilance)

collection and scientific evaluation of information on suspected adverse reactions related to the use of a medicinal product etc.

Environmental risk assessment required for all new applications (technical guidances available)

Obligation to report on environmental problems of veterinary medicinal products

Eco-Pharmacovigilance

within post marketing surveillance of a VMP

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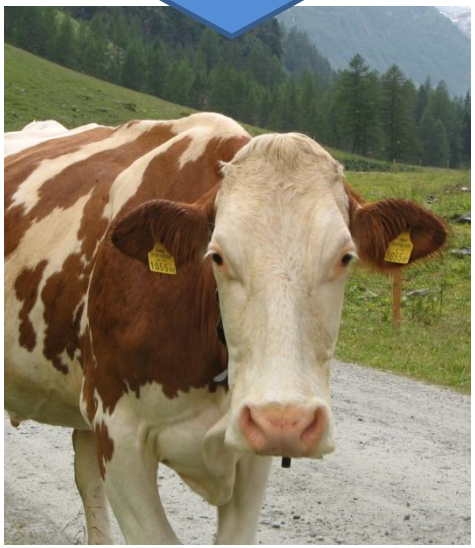
Medication



Spreading of manure

- How to observe potential environmental effects ?
- Evidence of the causal relationship ?

photos: Ines Rönnefahrt

Eco-Pharmacovigilance

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There is a discrepancy between the general obligation to report on potential environmental problems and the question how to fulfill this obligation.

Occurrence, fate and effects in the environment are neither systematically monitored nor reported and evaluated.

Eco-Pharmacovigilance – a suitable concept for environmental safety?

How to ensure the environmental safety of pharmaceuticals ?

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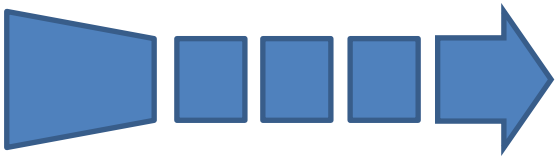
Pre market surveillance

administrative information and scientific documentation

Marketing approval



benefit-risk- analysis

Post market surveillance (pharmakovigilance)

collection and scientific evaluation of information on suspected adverse reactions related to the use of a medicinal product etc.

Detailed environmental risk assessment based on fate and effects data for every medicinal product resp. drug substance

(→ Monograph system)

Very limited possibilities:
- monitoring e.g. of the occurrance of active substances
- targeted verification of identified risks under field conditions

Monograph system on active pharmaceutical substances

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→ Collection and scientific evaluation of data

Content of a monograph:

- Data requirements according to EMA guidelines for ERA: physical-chemical data, fate & effects data
- Information on mode of action
- Information on metabolism & excretion by patients
- Additional information available in the public domain (monitoring data, published research data etc.)

Data allow a first identification of potential environmental hazards.

Monograph system on active pharmaceutical substances

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Advantages:

- ***Robust information*** on fate and effects of the substances in the environment
- ***Harmonization*** of ERAs of similar products
- Offers opportunity for ***publication of data*** (endpoints!) in a harmonised format
- Prevents repetition of experiments → Animal welfare, saving of testing material etc.
- Saves resources of applicants & authorities needed for application of a marketing authorisation (reduced financial burden)

Monographs ***should be updated regularely*** to adapt them to the scientific and technical progress !

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Summary

Summary pharmaceutical legislation

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ERA of veterinary pharmaceuticals is well established and is able to identify ‘substances of concern’.

Challenges for research and regulations still exists (antimicrobial resistance, hormons, effects caused by permanent low-level exposure etc.)

Monograph-System on active pharmaceutical substances should be established.

- important base for ensuring environmental safety of VMPs
- should be updated regularely
- allows harmonized ERAs on similar products
- offers better availability of data in a harmonized form

Summary

Data on environmental fate and ecotoxicological effects are the essential basis for any kind of identification and management of risks and should therefore be adequately available. - **Publication** in Public Assessment Reports on medicinal products and/or monographs on drug substances are important.

Risk management strategies should focus on prevention and the implementation of the precautionary principle. Risk communication to all concerned parties is essential.

Adaptation of the **pharmacovigilance system** to environmental issues.

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Thanks for your attention!

Many thanks to my colleagues (UBA, Section IV 2.2)