



Federal Environment Agency, Dessau-Roßlau

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

Ines Rönnefahrt

**Federal Environment Agency (UBA), Germany**

**International Workshop on Eco-Pharmacovigilance of  
Veterinary Medicinal Products, Berlin 4.-5.12.2013**

Umwelt  
Bundesamt 




# What this talk is about ...

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



# Administration in Germany

 Federal Ministry for the Environment, Nature Conservation and Nuclear Safety



UBA

 Federal Ministry of Food, Agriculture and Consumer Protection



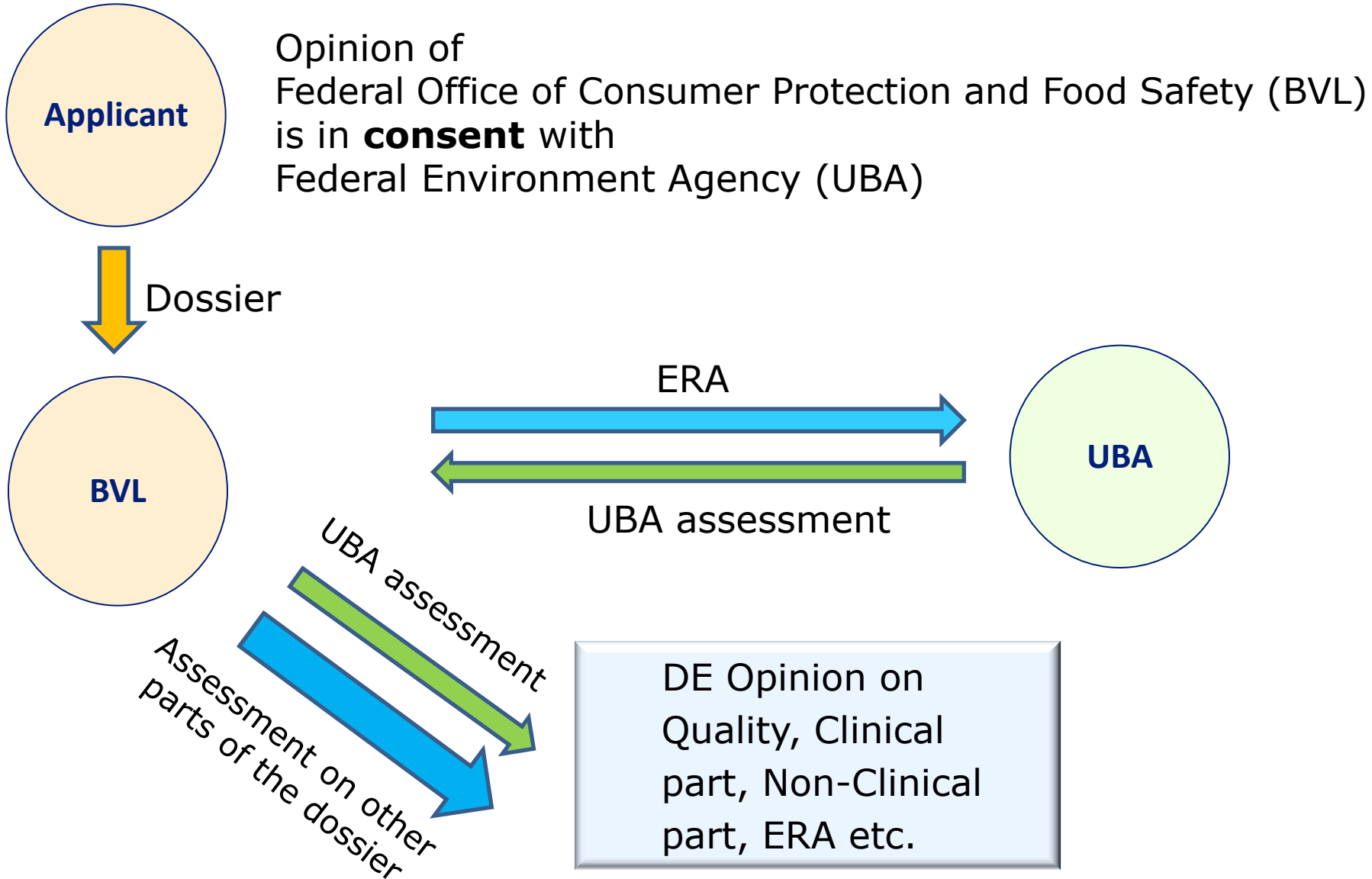
 Federal Office of Consumer Protection and Food Safety

BVL

ERA of VMPs  
←→



# Administration in Germany

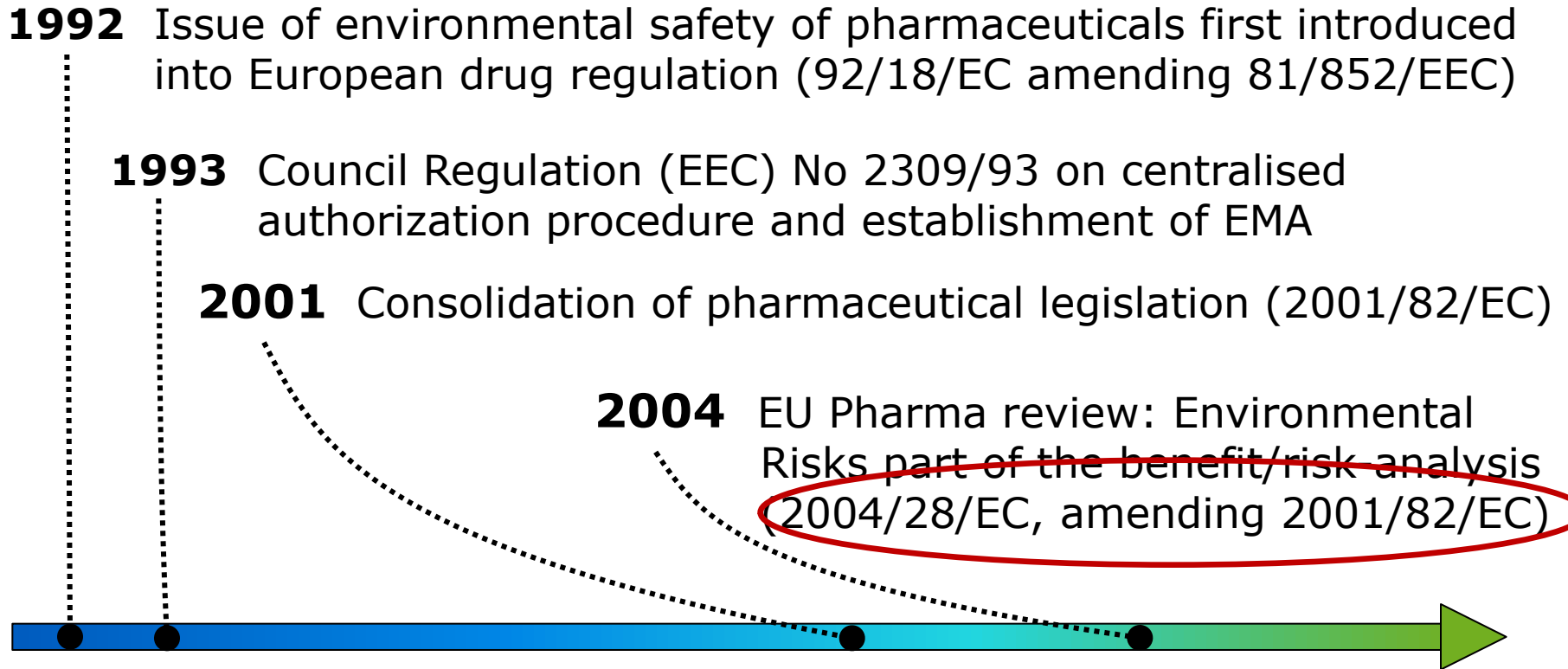




# Legal background



# Legal background



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



# Legal background

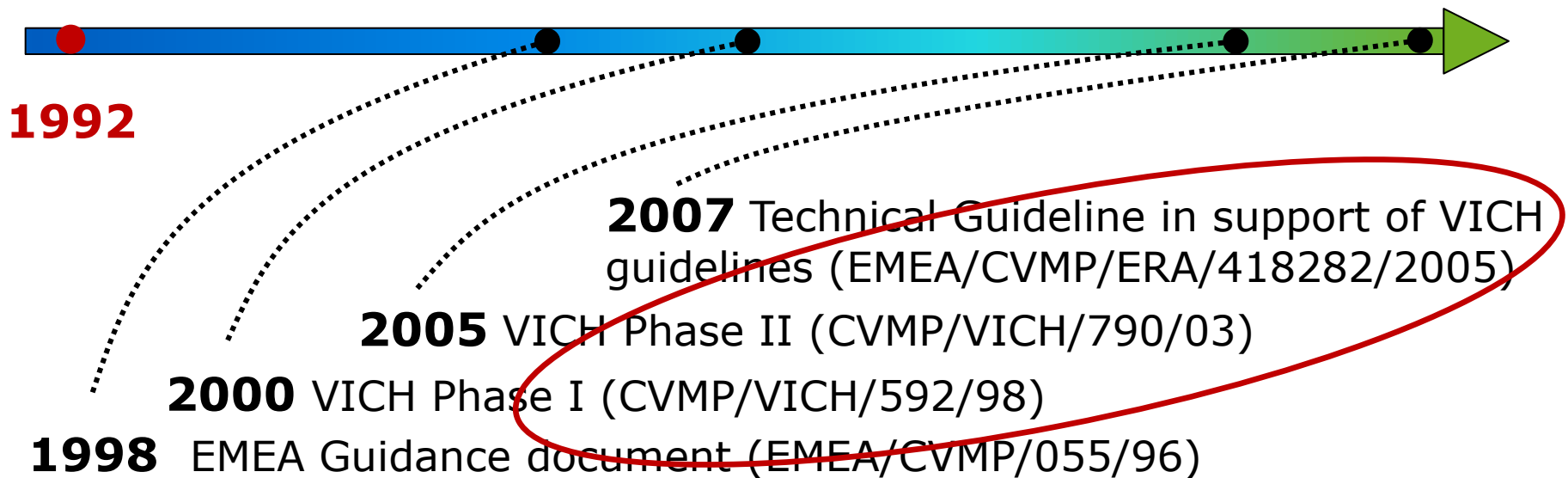
(Directive 2001/82/EC as amended in 2004)

- 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

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







# **Environmental risk assessment** according to EMA-Guidelines



**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?

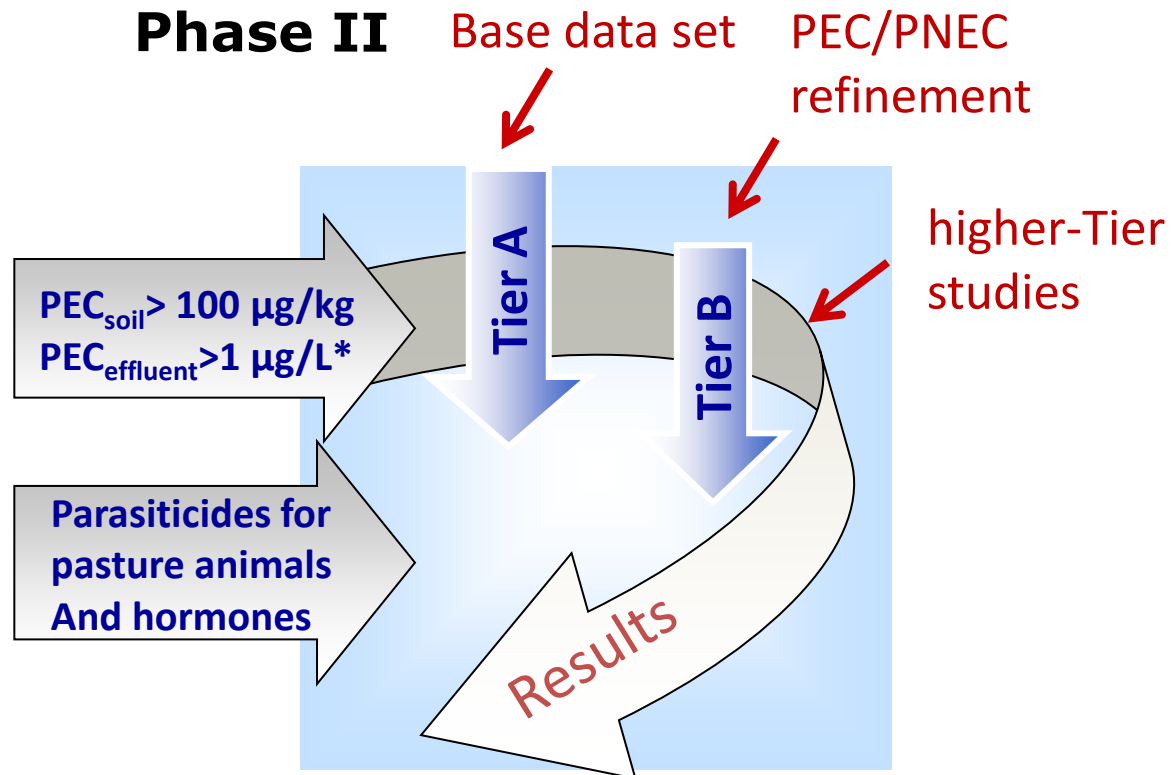
## Phase I

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



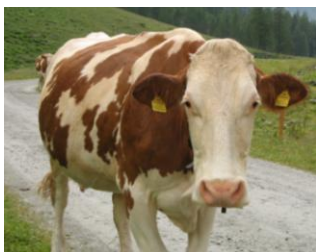
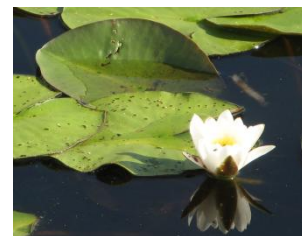
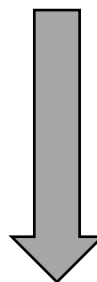
**No relevant exposure  
-> no further assessment**

## Phase II



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

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



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



**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)



# **Experiences with Environmental risk assessment**



# UBA experiences with ERA

- 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:
  - Parasitocides:** 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

- Effect assessment within the EMA guidances is effective for most drug classes, but:
- Effect assessment of antimicrobials?
  - Tailored risk assessment for hormones?
  - Effects of life-long exposure to very low levels of pharmaceuticals?  
→ No methods are available to evaluate such effects!



Challenges for future research and regulation !



# UBA experiences with ERA

- 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 !





# **Authorisation procedure & Eco-Pharmacovigilance**



# Environmental risk assessment in the authorization procedure

## 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

Medication



Spreading of manure

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



# Eco-Pharmacovigilance

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 ?

## Pre market surveillance

administrative information and scientific documentation



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

**(→ Monograph system)**



## Post market surveillance (pharmakovigilance)

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



Very limited possibilities:

- monitoring e.g. of the occurrence of active substances
- targeted verification of identified risks under field conditions



# Monograph system on active pharmaceutical substances

→ 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

## 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 regularly** to adapt them to the scientific and technical progress !



# Summary





# Summary pharmaceutical legislation

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

Challenges for research and regulations still exists (antimicrobial resistance, hormones, 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 regularly
- 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.

**Thanks for your attention!**

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

