Bundesamt für
Verbraucherschutz und
Lebensmittelsicherheit

Legal base and experience with Pharmacovigilance of potential environmental problems

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Pharmacovigilance Definition

The science and activities relating to the **detection, assessment, understanding** and **prevention** of adverse effects or any other drug-related problem.

WHO

Scope

What is special about Veterinary Pharmacovigilance?

larger scope than human pharmacovigilance

„protect public and animal health“

Guideline for Pharmacovigilance of Veterinary Medicinal Products, Volume 9B

„assessment of potential risks to human or animal health or to the environment“

Council Directive 2004/28 EC Art. 33

Scope

Veterinary Pharmacovigilance covers not only clinical safety in animals, but also other aspects of post authorisation surveillance

but primary objective: collect and evaluate information on suspected adverse drug reactions (ADRs): serious, non-serious, expected, unexpected,

and from periodic safety update reports (PSURs)

Scope

includes also

- → lack of expected efficacy
- → off label use / misuse / abuse
- → insufficient withdrawal periods, food safety
- → potential environmental problems
- → adverse reactions in humans to veterinary medicines (user safety aspects)

Scope

At authorisation:
assessment of quality, efficacy and safety

but

limited number of animals in clinical trials and field studies

(several hundred – or thousand animals)

Scope

therefore surveillance after authorisation, under conditions in practice

example

statistics: adverse reaction with frequency of 1:10.000

for detection with 95% certainty at least 30.000 animals must be tested !!!

Scope

improve knowledge base for veterinary medicines in the post-marketing period

- most ADRs not demonstrated in clinical trials
  - ☆ species and breed specific reactions
  - ☆ age related reactions
  - ☆ rare but serious ADRs
  - ☆ incidence rates
  - ☆ potential reactions in humans using the veterinary medicinal products

Legal base European Union

Human and veterinary

⇨ Council Regulation 726/2004/EC, joint legislation
Chapter 3, Articles 41-48
since 2012 new legislation for human medicines

⇨ Council Regulation 540/95/EC

Veterinary

⇨ Council Directive 2004/28/EC
Title VII, Articles 72-79

⇨ Guidelines Volume 9B “The Rules Governing Medicinal Products in the EU” , final 2011

Volume 9B Part I Guidelines for Marketing Authorisation Holders (MAH) 4.3.2 Reporting on potential environmental problems

⇨ A potential environmental problem: a situation where animals of non target species, other animals, human beings or plants are suspected to be adversely affected through exposure to a Veterinary Medicinal Product (VMP) present in the environment

⇨ Any suspected environmental problem related to a VMP should be recorded by the MAH as soon as comes to his knowledge

Volume 9B Part I Guidelines for Marketing Authorisation Holders (MAH) 4.3.2

Minimum requirements for potential environmental problem report:

- ⇨ the location
- ⇨ the animal or plant involved
- ⇨ the nature of the suspected environmental problem
- ⇨ the suspected product (s)

Volume 9B Part I Guidelines for Marketing Authorisation Holders (MAH) 4.3.2

Reports should not normally be expedited = 15 days reports, but should be discussed in PSUR:

⇨ However in specific circumstances: to limit further environmental damage and to evaluate the benefit-risk balance, reports of environmental problems should be reported promptly to the Authorities

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Legal base-European Union
Definitions: Council directive 2004/28/EC

adverse reaction	harmful and unintended reaction at normally used doses
serious adverse reaction	fatal, life-threatening, lesion-producing, significantly disabling or incapacitating, congenital anomaly/birth defect, resulting in permanent or prolonged signs
unexpected adverse reaction	adverse reaction the nature, outcome and severity of which is not consistent with the Summary of Product Characteristics (SPC)

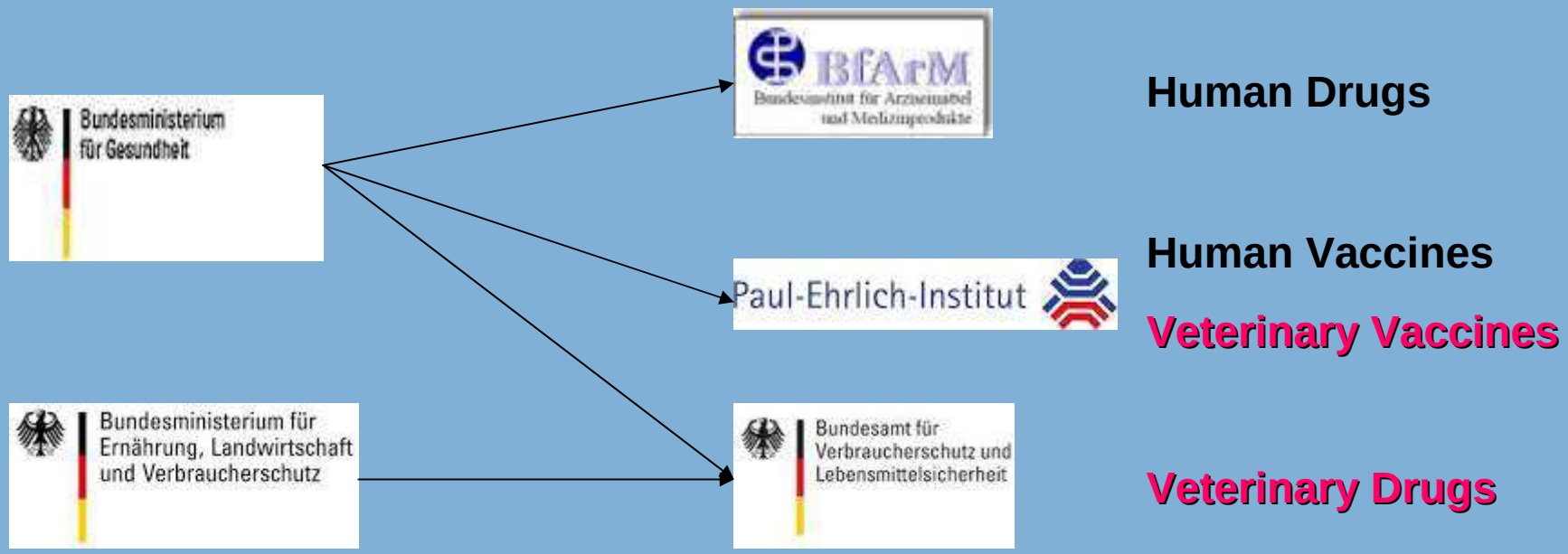
Legal base- European Union
Definitions continued

PSURs	periodical reports containing the records referred to in Article 75
post-authorisation safety study	pharmacoepidemiological study or clinical trial to identify/investigate a safety hazard
human adverse reaction	noxious and unintended reaction in humans after exposure to a veterinary medicinal product

Legal base in Germany

Who is responsible for Veterinary Medicines?

Ministries **Federal Agencies**

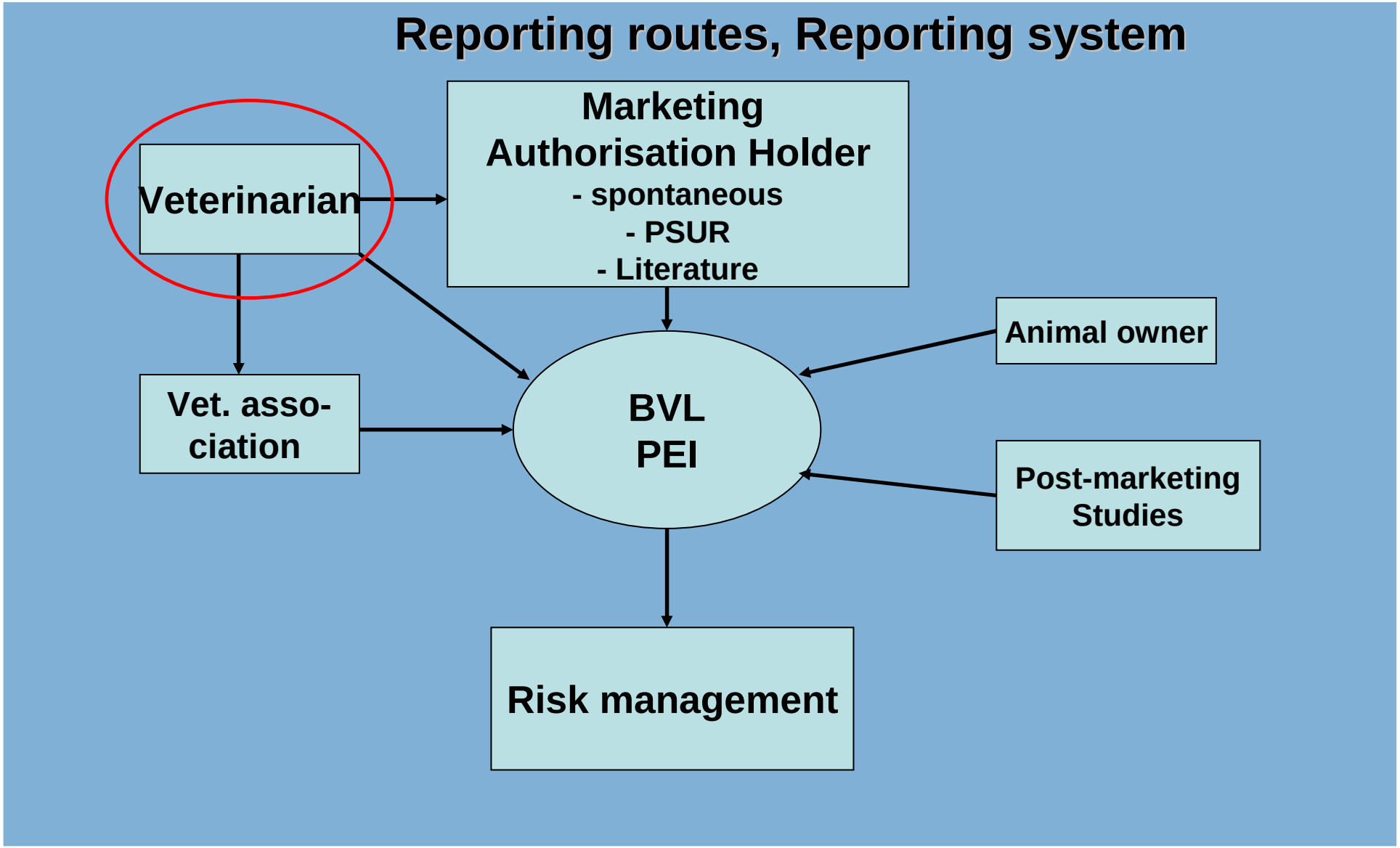


Human Drugs

Human Vaccines

Veterinary Vaccines

Veterinary Drugs


Reporting routes, Reporting system
Marketing Authorisation Holder
- spontaneous
- PSUR
- Literature
Veterinarian
Vet. asso-ciation
BVL
PEI
Animal owner
Post-marketing Studies
Risk management

Particularities of Veterinary Pharmacovigilance

2 categories:

companion animals ⟺ food producing animals

emotional value ⟺ economic value

medical/ethical aspects : valid for both

Particularities of Veterinary Pharmacovigilance

What kind of differences?

In Species:

- Differences in drug metabolism for ruminant and monogastric animals
- Enzymes
  - Lack of glucuronidases in cats
- Sensitivities
  - Dexamethason induced laminitis in horses
  - Penicillin intolerance in guinea pigs
  - Avermectin intolerance in collies and turtles

What kind of differences?

In Breeds: MDR1-Defect

Some breeds of dogs are more sensitive to certain drugs compared to other breeds. For example, Collies, Australian Shepherds and other breeds are often more sensitive to the antiparasitic drug, ivermectin and also to other substances.

Particularities of Veterinary Pharmacovigilance

off label use:

- in minor species and for minor uses quite common in veterinary medicine, no authorised products available → therapeutic gaps
- use of human drugs in small animals (dogs and cats)

Particularities of Veterinary Pharmacovigilance

insufficient withdrawal period: food safety problem
residues of drugs in food, violation of Maximum Residue Limits (MRL)

environmental problems DE

Sheep dip solution (Phoxim) accidentally contaminated small river and led to fish death (lamprey, moray, trout)

Fish consumption from this area suspended for 6 weeks

Particularities of Veterinary Pharmacovigilance

environmental problems FR

Fish in small pond all found dead. On bank of pond one empty syringe of Prilium (Imidaprilum) = heart medication for dogs, was found. Case is unclassified in database, causality seems unlikely

Particularities of Veterinary Pharmacovigilance

environmental problems DE, SI

In DE reports in pigs, related to vaccines, where infections with vaccine virus strain of PRRS apparently excreted in the environment, had been reported in animals from neighbouring herds

In SI a fox displayed rabies symptoms after vaccination with oral baits in the region, vaccine strain confirmed in tests

environmental problems SE

Dog poisoned with Pentobarbital by licking blood mixed liquid from nostrils of euthanised horse. Dog displayed convulsions, ataxia, irregular pulse, somnolence

Dog recovered after treatment in intensive care. Causality is probable in relation to exposure

Particularities of Veterinary Pharmacovigilance

environmental problems FR

Vultures exposed to a horse carcass, euthanised with Pentobarbital, displayed lethargy, somnolence, excitation, muscle tremor. One bird died. Strong time and circumstantial evidence, symptoms consistent with pentobarbital action on central nervous system

Causality is classified possible

environmental problems, Brazil

Chicken found dead or some with apathy and salivation after supposedly eating rice bran from horses feces. 2 horses on farm had been treated the day before with trichlorphos for deworming. Case considered unlikely, as substance is almost completely resorbed during gastro-intestinal passage, other explanations possible.

Particularities of Veterinary Pharmacovigilance

environmental problems India, Pakistan

Diclofenac, used in Southern Asia as a livestock treatment, is toxic to vultures when they feed on contaminated carcasses, causing kidney failure and death in birds

Particularities of Veterinary Pharmacovigilance

environmental problems India, Pakistan

3 vulture species are nearly extinct. In India breeding programmes in captivity are established. The use of Diclofenac in livestock is forbidden, but insufficient controls of sales as chemical

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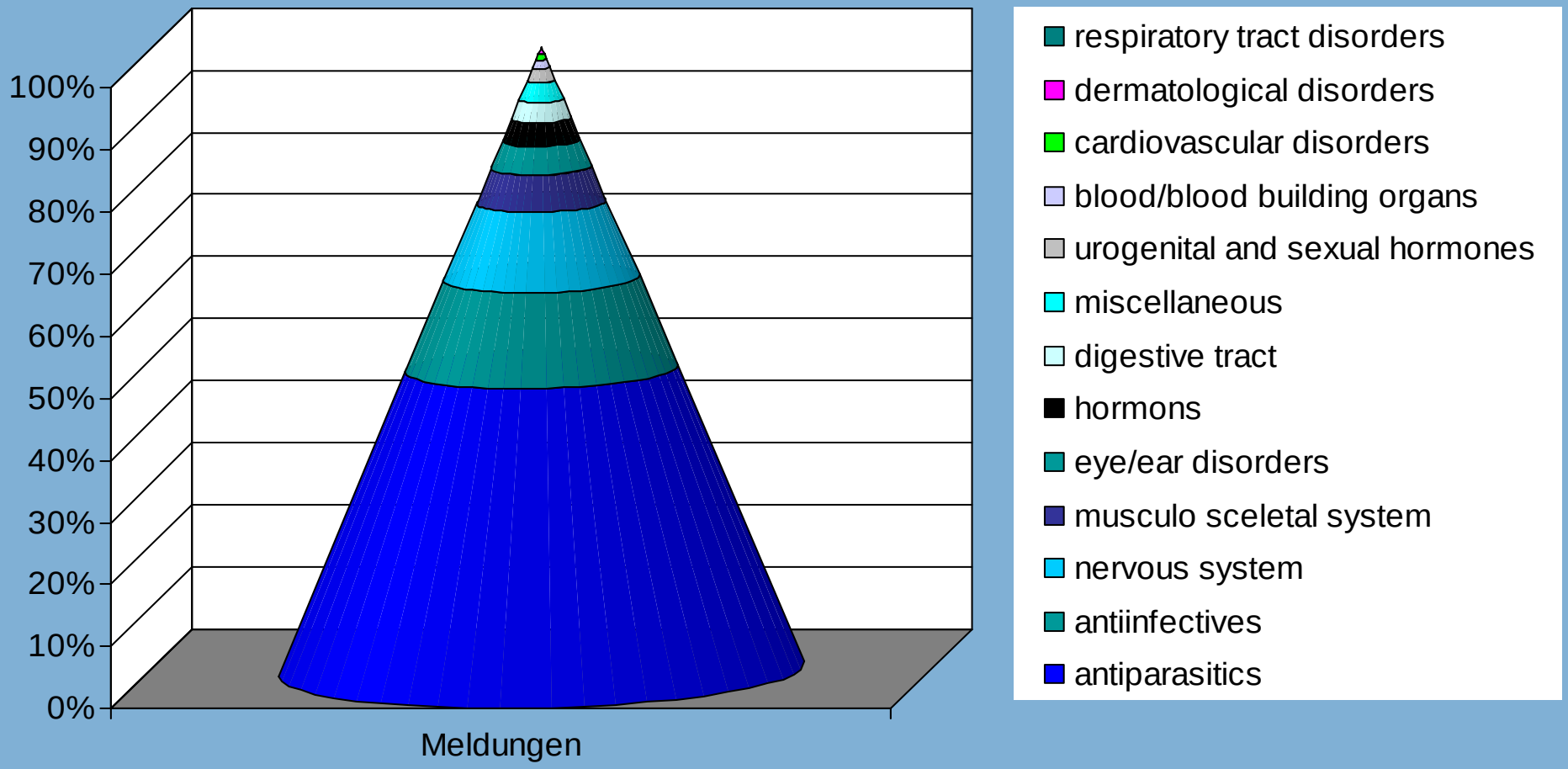
Adverse reactions in animals BVL 2012

Anatomical-therapeutic-chemical classification system (ATCvet-Code)



Human safety aspects

Directive 2004/28/EC and Vol. 9 B state:
any human reaction is to be treated as serious and must be received as expedited reports in 15 days

classes of substances involved mainly:

- ectoparasiticides
- vaccines and other injectable products (accidental exposure)

Adverse reactions in humans

symptoms observed most frequently:

- skin reactions: rash, pruritus, eczema
- respiratory symptoms: cough, breathing anomalities, bronchitis, asthmatic crisis
- gastro-intestinal symptoms: nausea, vomiting, diarrhea
- neurological symptoms: ataxia, trembling, lethargy, fatigue, depression

Adverse reactions in humans

Unintended

- close contact with animal i.e. antiparasitic spot on products, collars
- contact (skin / eye)
- accidental injection
- confusion with human medicinal product i.e. Clomipramine, Enalapril

Misuse / Abuse

- Suicidal intention with euthanasia products (pentobarbital, embutramid mebezoniumjodid)
- drug abuse of ketamine in discotheques for hallucinogenic effects

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Résumé for ecotoxicity reports

Most of few ecotoxicity cases in PHV database are accidental exposure or poisoning events

Spontaneous reporting system can only give isolated sporadic data

Pharmacovigilance- as a condition for authorisation?

- Post Authorisation Safety Studies (PASS) as tool

- little experience so far
- Guideline from human medicine GVP Module VIII
- in Volume 9B only general advice, to be completed with regard to special requirements in veterinary medicine
- in future more frequent use to clarify potential or identified risks after authorisation

Thank you for your attention!