Shared Facilities Workshop – Case Study, Application of HBEL in a Cleaning Validation

Dr. Andreas Engwicht-Lassmann, Bayer Animal Health, on behalf of IFAH Europe

What makes the difference…

Europe IFAH
Representing the European Animal Health Industry

Human vs Veterinary Pharmaceuticals

- **Broad spectrum of animal species and body shapes**
  - **We have medicines for kittens (< 1 kg) and adult cows (> 500 kg)!**
  - **Some animal species react different on API (e. g. Febantel or Permethrin are toxic for cats but not for dogs)**
- **The problem with the Ectoparasiticides**
  - **In most cases no dosage – spot on, pour on, dips**
  - **Exempted from GMP – HBEL data missing**
  - **But: often very toxic substances!**
- **Human and Veterinary on shared facilities**
  - **Animal species react differently on API for humans**
  - **Different dose masses – ½ ton cow vs 70 kg human**

How do we manage this complexity

4 steps through the complex exercise

Planning a cleaning validation for a manufacturing vessel with

- **Human and veterinary pharmaceuticals**
- **A topical human drug product without dose**
- **An oral nutritional product with toddlers as target patient**
- **Oral veterinary products with dog puppies as target species**

How we manage this complexity

Step 1 – Have the prerequisites ready

- **Check leaflets for doses and treatment frequencies**
- **Have HBEL ready – we have chosen to use PDE**
  - **PDE may be either derived from ADI or OEL values or calculated following toxicological literature research and following the requirements of EU guideline.**
- **Considerations for PDE choice were**
  - **Target animals (puppies, kittens) → PDE x 1 kg**
  - **Toddlers involved → PDE x 3 kg**
  - **Animal species specific effects → safety factor?**
  - **Route of administration (topical, oral, skin with lesions)**
- **Analytical methods with sufficiently low levels of quantification**

How we manage this complexity

Step 2 – determine the worst case consecutive product

- **Calculate the dose mass using a quotient calculated from product batch size and mass of the daily doses applied.**
  - **Difficult when no dose is given, e. g. for some topical dosage forms for Animal Health products**
- **The product with the lowest quotient is the worst case product and is chosen as the consecutive product for the study.**
- **The next critical product will be chosen as consecutive product for the worst case product.**

How we manage this complexity

Step 3 – determine the acceptance criteria

- **Calculate maximum allowable contamination based on PDE, 1/1000 dose, ppm (when no dose available).**
- **Choose the strictest of the values as target for the study.**
- **Conduct a risk assessment to determine how many validation runs per product / cleaning method and how to sample.**

How we manage this complexity

Step 4 – Execute the exercise!

- **As the experience shows, the PDE based limits often allow much more residues than the 1/1000 dose criteria or 10 ppm.**
- **Competent authorities would surely not allow to loosen criteria when switching completely to PDE or other HBEL?**

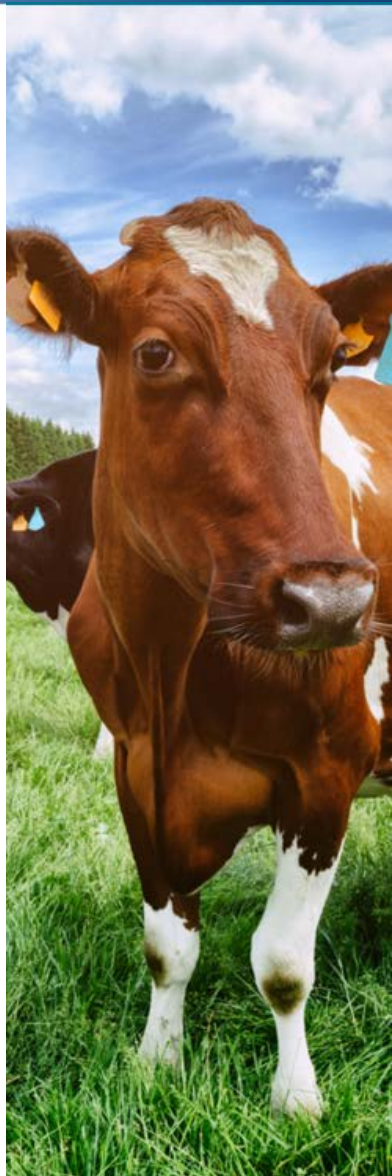
Conclusions we made

We managed the complex exercise!

- **Analytical results of cleaning validation are very often far below the allowed residues.**
- **Analytical methods often allow determination of very low residues.**
- **There are many assumptions to be made in forehand**
  - Animal species, body weights
  - Specific conditions of administration → skin lesions
  - Specific risks of contamination depending on the equipment

Expectations from workshop

- **Inspectors gain trust in cross contamination control activities of (vet) industry**
- **Clear guidance for open issues through Q&A document with regard to specifities for veterinary pharmaceutical industry**
  - When to consider animal species specific toxicological API profiles
  - How to consider specific conditions in application route
  - How to compensate for the broad variety of body weights of target animals
  - How to consider sharing facilities between human and veterinary products
  - How to deal with ectoparasiticides when no dose is given (spot-on, pour on, emulsion concentrates etc.)
- **Better understanding on Inspectors‘ side for the specifities of the vet industry**



Next Steps

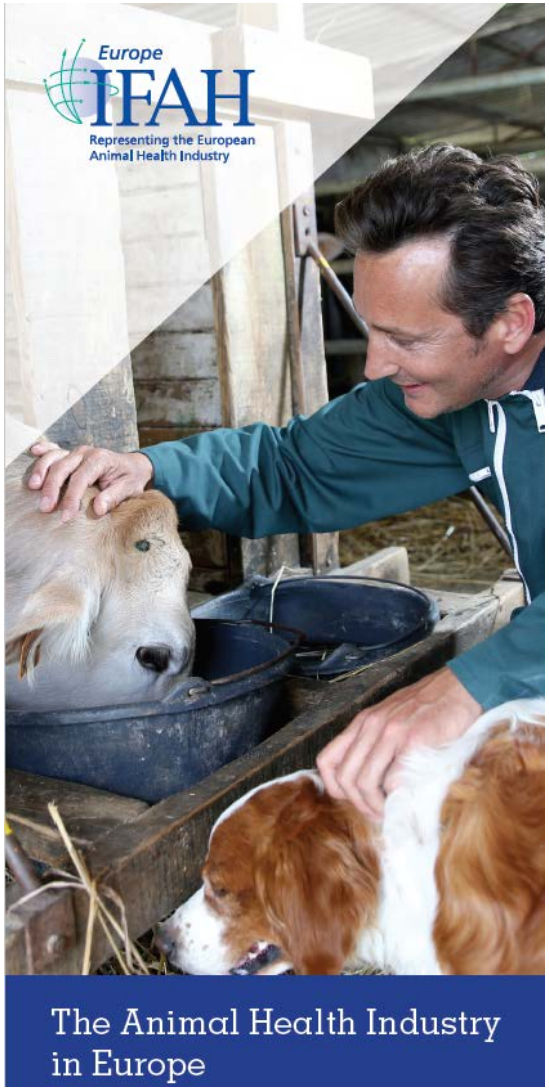
- **Veterinary Industry would welcome to open the discussion for amendment of Annex 4 in order to reflect:**
  - Specifities of veterinary pharmaceuticals
  - Considerations of new cross contamination rules for the manufacture of human and veterinary drug products on shared equipment
- **Annex 4 is now one of the oldest GMP documents in Eudralex Vol. 4 and needs an upgrade to current GMP environment**
- **All annexes have been updated to reflect new cross contamination rules / risk assessments**
- **A separate workshop would be recommended for the veterinary industry**

Thank you

Europe IFAH
Representing the European Animal Health Industry

THANK YOU

Who we are



IFAH-Europe =

- originators and generics,
- large, medium-sized and small companies

-> research, develop & manufacture veterinary medicines

Protect health & welfare of over 1 bln animals & help to:

- Improve people's health and public health
- Contribute to sustainable production of safe & affordable food
- Contribute to a sustainable environment

Our mission:

- awareness of **value** of animal health to society
- promote a **predictable**, **harmonised**, **science-based** & **innovative** marketplace for **safe**, **effective** & **quality** veterinary medicines for vets, animals owners & farmers.