Veterinary knowledge for pharmacy students

Institute of Pharmaceutical Technology and Biopharmacy

THE PURPOSE OF ANIMAL HEALTH

- The protection of the health of animals
- Facilitating race-preservation
- Production enchancers
- Prevention of risk factors that may have influence on public health
- Economic aspects

POINTS OF CONNECTIONS OF ANIMAL HEALTH AND PHARMACEUTICS

- Veterinary medicine marketing and distribution
- Pharmacovigilance system
- Production of veterinary medicine
- Quality assurance, quality control, marketing authorizations
- Prophylactic activities
- Prevention of zoonoses
- POSOLOGY - study of drug administration

Medicinal Products for Human and Veterinary Use

comparison of medical productions

SIMILARITY

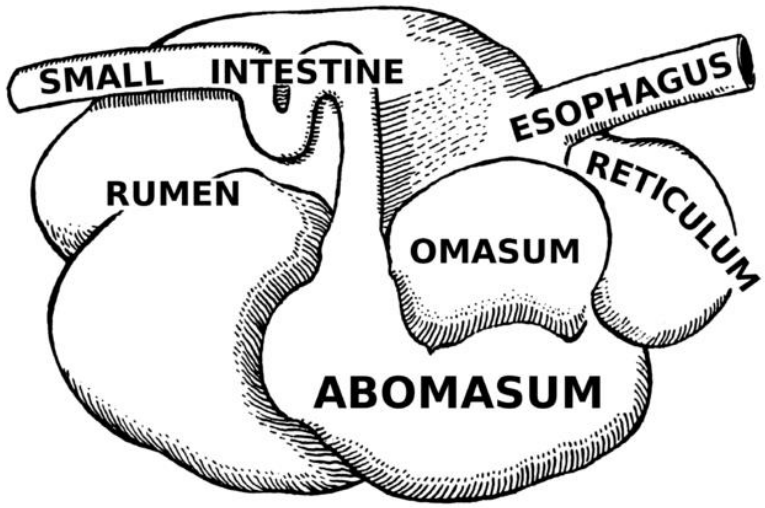
- GMP
- quality assurance, quality control
- precise dosing
- stability

DIFFERENCE

- Special dosage forms (intramammary, collars)
- MRL value, withdrawal periods
- species-specific
- multi dose preparations

Anatomical arrangement of the GI tract

- **Ruminant species** →
  - Cattle
  - Sheep
  - Goat

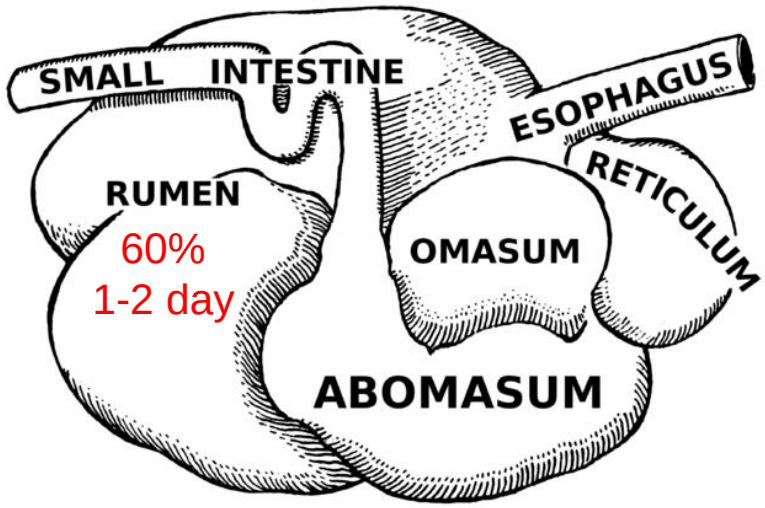


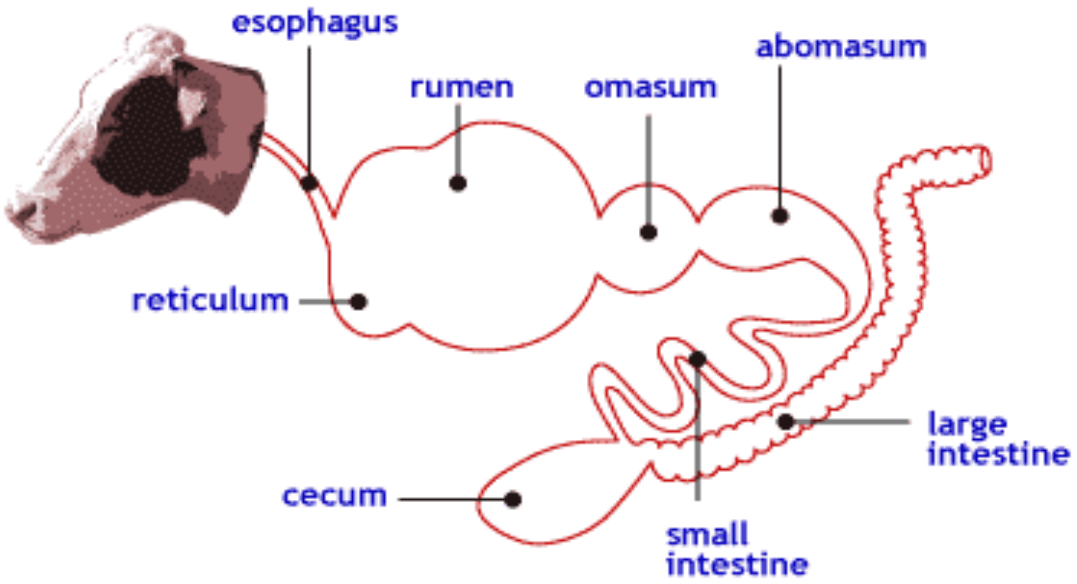
- **Monogastric species**
  - Horse
  - Pig
  - Dog
  - Cat

Anatomical arrangement of the GI tract

Turnover 1-2 day

‘After comminution by rechewing and microbial digestion, the liquid component with suspended particles of reticuloruminal contents is ‘‘pumped’’ by the omasum (third compartment of the forestomach) into the abomasum’ (true stomach)





Anatomical arrangement of the GI tract

Specialities:

- Horse
  - gastric pH is 4.5-6
  - no gall bladder (camels and giraffes)
  - sensitive to production enhancer/growth promotant
- Pig
  - sensitive to production enhancer/growth
- Cattle
  - sensitive to production enhancer/growth promotant
- Ruminants
  - saliva does not contain amylase and have antifoaming effect (avoid from bloating)

Anatomical arrangement of the GI tract

	Relative capacity (%)		
Component	Horse	Pig	Dog
Stomach	8.5	29.2	62.3
Small intestine	30.2	33.5	23.3
Cecum	15.9	5.6	1.3
Large colon	38.4	31.7	13.1
Small colon and rectum	7.0		

	Relative capacity (%)
Component	(Sheep and Goat)
Rumen	52.9
Reticulum	4.5
Omasum	2.0
Abomasum	7.5
Small intestine	20.4
Cecum	2.3
Colon and rectum	10.4

Anatomical arrangement of the GI tract

pH of urine:

- **Herbivorous** species (7.2-8.4)
- **Carnivorous** species (5.5-7.0)
- **Omnivorous** species (4.5-8.2)

Reproductive (estrous) cycle

- Influenced by photoperiod
- Periodicity

pH of the GI tract:

- Weak acids with pKa values above 3.0 and bases with pKa values below 7.8 are well-absorbed from the small intestine
- At pH values below the pKa, weak acids exist primarily in the non-ionized form, which is the moiety that can readily be absorbed; the converse applies to weak bases.

Biopharmacy

The mechanisms of action of drugs appear to be the same in mammalian species.

- Plasm protein binding:
  lower binding of (especially) acidic drugs in birds
- Metabolism:

Domestic animal species with defects in certain conjugation reactions			
Species	Conjugation reaction	Major target groups	State of synthetic reaction
Cat	Glucuronide synthesis	-OH, -COOH, $-NH_2$, =NH, -SH	Present, slow rate
Dog	Acetylation	Ar-NH_2	Absent
Pig	Sulfate conjugation	Ar-OH, Ar-NH_2	Present, low extent

- Elimination:
  avian and reptilian species have a well-developed renal sys.
  Herbivores > carnivores > human

Biopharmacy

Challenges facing veterinary drug product development

- Enormous **diversity in size, behavior**, metabolic needs, and lifespan among animal species
- Species and breed differences in both **pharmacokinetic** and toxicity profiles
- A wide spectrum of disease **agents** that produce different disease manifestations under different conditions
- A range of **husbandry practices**, which includes a variety of settings in which animals are kept - ranging from animal companions in the home to large livestock operations
- **Lack** of ability to directly **communicate** with and educate the animal patient
- **Economic constrains**
- **Public health concerns**

Route of administration of veterinary products

	Application
Externally	rostra/beak bathing atomization (ophthalmology) spot on pour on dip in bovine teat treatment
Internally	Injection into the terminal leg the ruga/fold of the wing Mix into the drinking water Spraying the feedingstuff Intramammal (udder) Intraruminal (rumen) Paravertebral (beside the spine) Oculonasal (eye and nose therapy)

Dosage forms

Dosage form	% of sale
Feed premix	35
Injectables	33
Oral tablets, Capsule, Bolus	09
Oral liquids, Powders	08
Topical	05
Implants	04
Paste, gels	03
Intramammary	02

Oral dosage forms available for administration to animals include oral solutions, liquids, suspensions, gels, pastes, capsules, tablets, ruminal boluses, powders and granules for addition to feed, soluble powders for addition to drinking water or fish medicating baths, and premixes for addition to feed for livestock or poultry.

Dosage forms

- *Liquid dose forms*: all animal species
- *Pellets and granules*: horses and cattle and swine
- *Tablets, capsules and boluses*: dogs and cats (The dosage form is placed on the back of the pet's tongue and its mouth is held shut)
- *Drenches:* horses and ruminants
- *Medicated water*: swine, cattle, poultry, and fish
- *Medicated feeds*: cattle, swine, horse, poultry, and fish. (type A, type B, type C)
- *Injectable products:* all animal species
- *Topical products*: for most animal species.
- *Medicated collars and ear tags*: dogs and cats (antiparasitic effect)
- *Intramammary preparations and vaginal inserts*: treatment of mastitis-related claims

Dosage forms of Ph. Eur. for veterinary use

Premixes for medicated feeding stuffs for veterinary use

(Praeadmixta ad alimenta medicata ad usum veterinarium)

Mixtures of one or more active substances, usually in suitable bases, that are prepared to facilitate feeding the active substances to animals. They are used exclusively in the preparation of medicated feeding stuffs.

Premixes occur in granulated, powdered, semi-solid or liquid form.

Used as powders or granules, they are free-flowing and homogeneous; any aggregates break apart during normal handling.

Used in liquid form, they are homogeneous suspensions or solutions which may be obtained from thixotropic gels or structured liquids. The particle size and other properties are such as to ensure uniform distribution of the active substance(s) in the final feed.

Unless otherwise justified and authorised, the instructions for use state that the concentration of a premix in granulated or powdered form is at least 0.5 per cent in the medicated feeding stuff.

Dosage forms of Ph. Eur. for veterinary use

Premixes for medicated feeding stuffs for veterinary use

(Praeadmixta ad alimenta medicata ad usum veterinarium)

Aim: facilitate the administration of the API

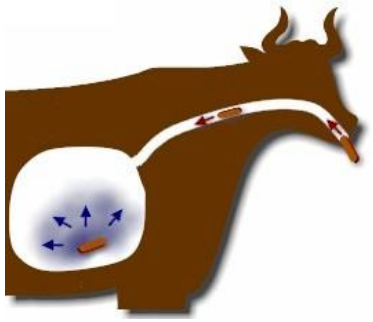
The label states :

- the category of animal for which the premix is intended,
- the instructions for the preparation of the medicated feeding stuffs from the premix and the basic feed,
- where applicable, the time that must elapse between the cessation of feeding of the medicated feeding stuff and collection of the material intended for human consumption.

Dosage forms of Ph. Eur. for veterinary use

Intraruminal devices

(Praeparationes intraruminales)



The requirements of this monograph do not apply to preparations (sometimes known as boluses), such as large conventional tablets, capsules or moulded dosage forms which give immediate or prolonged release of the active substance(s). Such preparations comply with the relevant parts of the monographs on Capsules or Tablets.

Intraruminal devices are **solid preparations** each containing one or more active substances. They are intended for **oral administration to ruminant animals** and are designed to be retained in the rumen to deliver the active substance(s) in **a continuous or pulsatile manner**. The period of release of the active substance(s) may vary from days to weeks according to the nature of the formulation and/or the delivery device.

Intraruminal devices may be **administered using a balling gun**. Some intraruminal devices are intended to **float** on the surface of the ruminal fluid while others are intended to **remain on the floor of the rumen** or reticulum. Each device has a density appropriate for its intended purpose.

Dosage forms of Ph. Eur. for veterinary use

Intraruminal devices

(Praeparationes intraruminales)

For **continuous release**, the intraruminal device is designed to release the active substance(s) at a defined rate over a defined period of time. This may be achieved by erosion, corrosion, diffusion, osmotic pressure or any other suitable chemical, physical or physico-chemical means.

For **pulsatile-release**, the intraruminal device is designed to release a specific quantity of active substance(s) at one or several defined intermediate times. This may be achieved by corrosion by ruminal fluids of the metallic elements of the intraruminal device which leads to sequential release of the constituent units which are usually in the form of tablets.

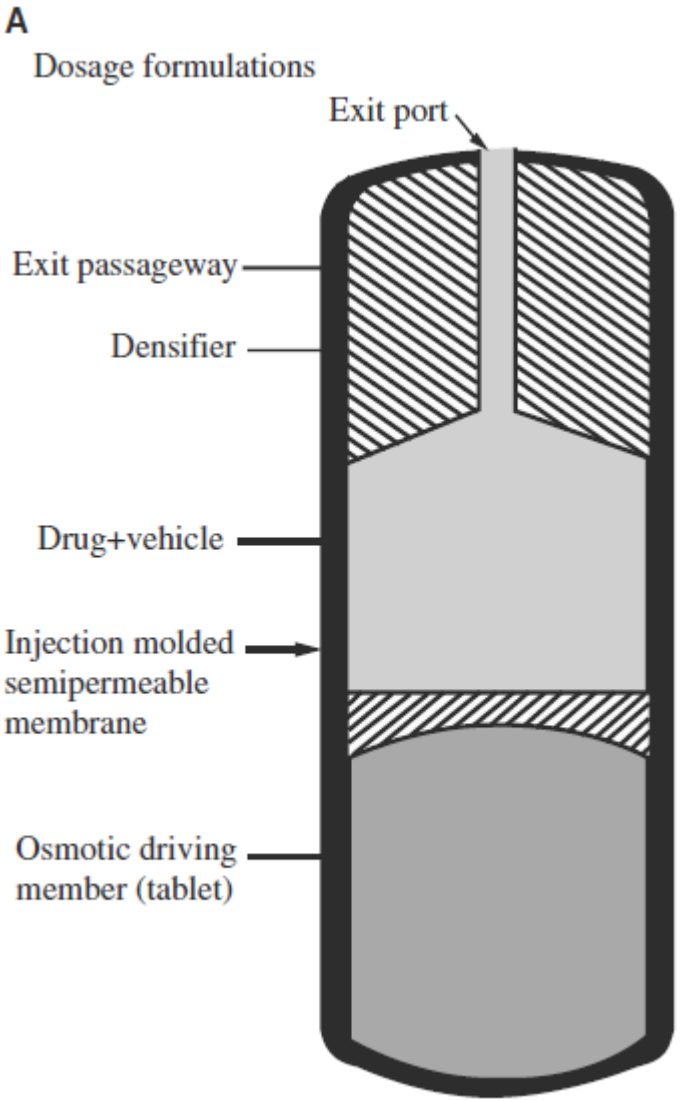
In the manufacture of intraruminal devices, means are taken to ensure an appropriate release of the active substance(s). In the manufacture, packaging, storage and distribution of intraruminal devices, suitable means are taken to ensure their microbial quality ; recommendations on this aspect are provided in the text on *Microbiological quality of pharmaceutical preparations*

The label states :

- for continuous-release devices, the dose released per unit time,
- for pulsatile-release devices, the dose released at specified times.

- **Intraruminal devices**

  (Praeparationes intraruminales)



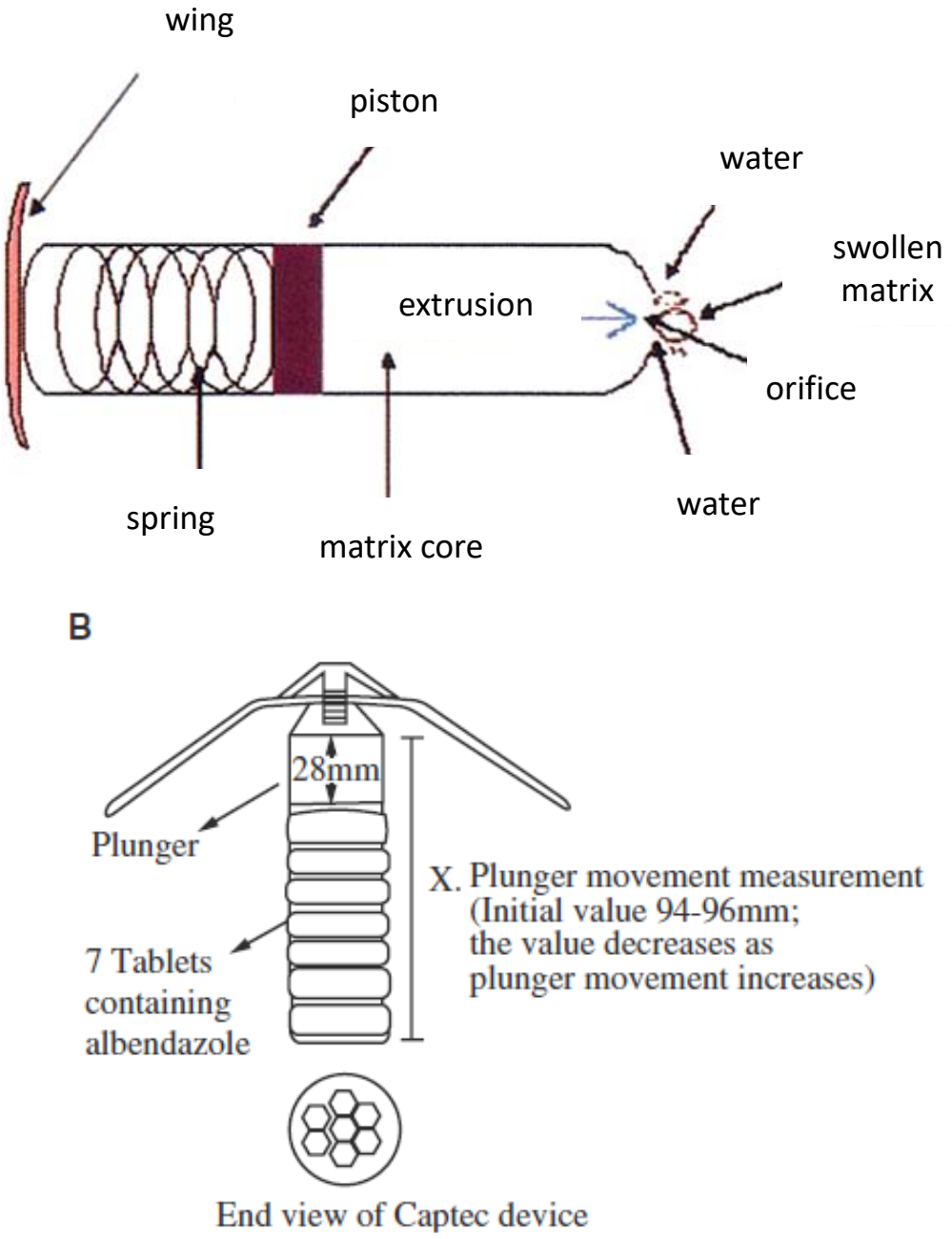


Fig. 2 (A) IVOMEC schematic; (B) captec schematic.

- **Intraruminal devices**

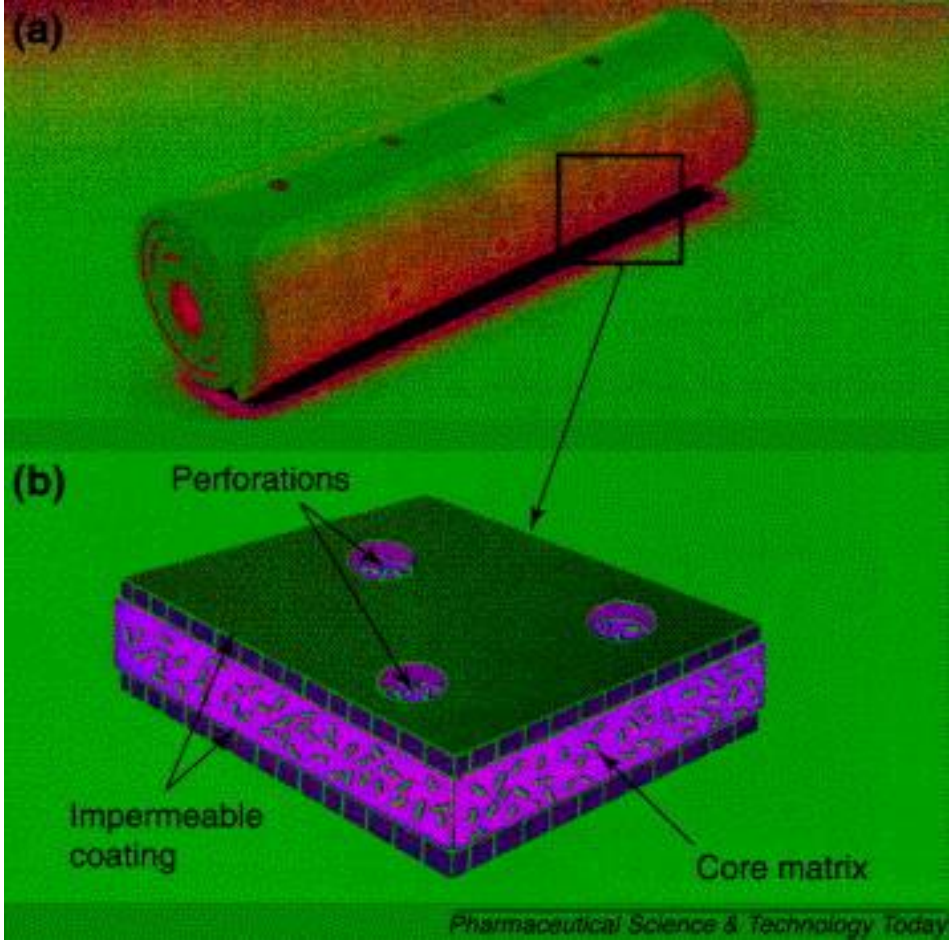
  (Praeparationes intraruminales)

Balling Gun

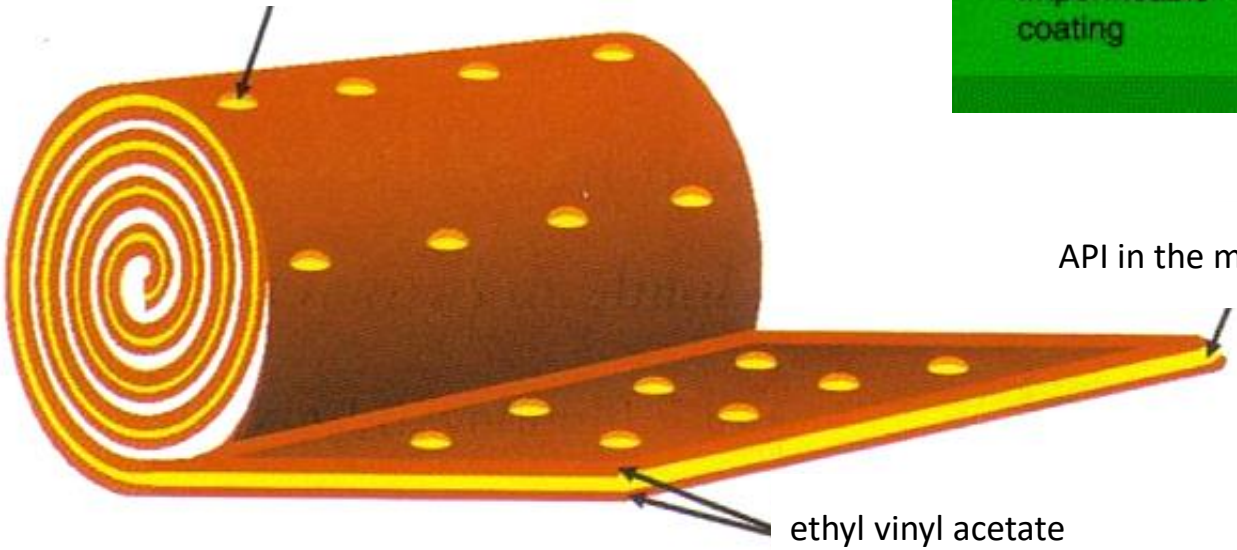
Liquid Drench Gun

- **Intraruminal devices**

  (Praeparationes intraruminales)



perforation (pores)



API in the matrix

ethyl vinyl acetate

- **Premixes for meticated feeding stuffs for veterinary use**

  (Praeadmixta ad alimenta medicata ad usum veterinarium)

- **Premixes for meticated feeding stuffs for veterinary use**

  (Praeadmixta ad alimenta medicata ad usum veterinarium)

Panacur SC 2.5%

Sheep body weight (kg)		10	15	20	25	30	35	40	45	50	55	60	65	70	75	80
Dose size	(ml)	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Doses per pack	1 litre	500	333	250	200	166	142	125	111	100	90	83	76	71	66	62
	2 litre	1000	666	500	400	333	285	250	222	200	181	166	153	142	133	125
	5 litre	2500	1666	1250	1000	833	714	625	555	500	454	416	384	357	333	312
	10 litre	5000	3333	2500	2000	1666	1428	1250	1111	1000	909	833	769	714	666	625

Above 80kg add 1ml for each additional 5kg bodyweight

Dosage forms of Ph. Eur. for veterinary use

Veterinary liquids praparations for cutaneous application

(Praeparationes liquidae veterinariae ad usum dermicum)

Unless otherwise justified and authorised, veterinary liquid preparations for cutaneous application comply with the requirements of the monograph on Liquid preparations for cutaneous application. In addition to these requirements, the following statements apply to veterinary liquid preparations for cutaneous application.

Veterinary liquid preparations for cutaneous application are liquid preparations intended to be applied to the skin to obtain a local and/or systemic effect. They are solutions, suspensions or emulsions which may contain one or more active substances in a suitable vehicle. They may be presented as concentrates in the form of wettable powders, pastes, solutions or suspensions, which are used to prepare diluted suspensions or emulsions of active substances. They may contain suitable antimicrobial preservatives, antioxidants and other excipients such as stabilisers, emulsifiers and thickeners.

Several categories of veterinary liquid preparations for cutaneous application may be distinguished :

- cutaneous foams
- dip concentrates
- pour-on preparations
- shampoos
- spot-on preparations
- sprays
- teat dips
- teat sprays
- udder-washes

Dosage forms of Ph. Eur. for veterinary use

Veterinary liquids praparations for cutaneous application

(Praeparationes liquidae veterinariae ad usum dermicum)

Dip concentrates are preparations containing one or more active substances, usually in the form of wettable powders, pastes, solutions or suspensions, which are used to prepare diluted solutions, suspensions or emulsions of active substances. The diluted preparations are applied by **complete immersion of the animal**.

Pour-on preparations contain one or more active substances for the prevention and treatment of ectoparasitic and/or endoparasitic infestations of animals. They are applied in volumes which are usually greater than 5 ml by pouring along the animal's dorsal midline.

Spot-on preparations contain one or more active substances for the prevention and treatment of ectoparasitic and/or endoparasitic infestations of animals. They are applied in volumes which are usually less than 10 ml, to a small area on the head or back, as appropriate, of the animal.

Dosage forms of Ph. Eur. for veterinary use

Veterinary liquids praparations for cutaneous application

(Praeparationes liquidae veterinariae ad usum dermicum)

Teat dips contain one or more disinfectant active substances, usually in the form of **solutions** into which the teats of an animal are dipped pre- and, where necessary, post-milking to reduce the population of pathogenic micro-organisms on the surfaces. Teat dips may be supplied/presented as **ready-to-use** preparations or they may be prepared by dilution of teat dip concentrates. Pre- and post-milking teat dips often differ in formulation. Teat dips usually contain emollients to promote skin hydration, to soften the skin and allow healing of lesions that would otherwise harbour bacteria.

Teat sprays contain one or more disinfectant active substances, usually in the form of **solutions** which are sprayed onto the teats of an animal pre- and, where necessary, post-milking to reduce the population of pathogenic micro-organisms on the surfaces. Teat sprays may be supplied/presented as **ready-to-use** preparations or they may be prepared by dilution of teat spray concentrates. Pre- and post-milking sprays often differ in formulation. Teat sprays usually contain emollients to promote skin hydration, to soften the skin and allow healing of lesions that would otherwise harbour bacteria.

Udder-washes contain one or more disinfectant active substances, usually in the form of **solutions** which are sprayed onto the udder and teats of an animal to remove mud and faecal contamination before the application of teat dips or sprays.
Udder-washes are usually prepared by the dilution either of concentrated preparations or of **ready-to-use** teat dips or teat sprays.

Veterinary liquids praparations for cutaneous application

(Praeparationes liquidae veterinariae ad usum dermicum)

Bovine mammary gland

- Antimicrobial agents, as with other drugs, cross the blood–milk barrier, which is a somewhat restrictive functional rather than anatomical barrier, primarily by passive diffusion.
- lipoidal blood–milk barrier (milk pH range 6.5–6.8)
  (tetracyclines, amphotericin-B, macrolides)

*An **ideal antimicrobial agent in bovine mastitis:***

- Low MIC
- High systemic bioavailability after IM inj.
- Lipid-soluble
- Low degree of protein binding
- Long half-life
- Minimal adverse effects
- Short withdrawal period (milk and slaughter)

penicillin G, amoxicillin, trihidrate-clavulenate)

Veterinary liquids praparations for cutaneous application

(Praeparationes liquidae veterinariae ad usum dermicum)

Percutaneous absorption

- The skin accounts for approximately 10% of live body weight in cattle, goats, and dogs; 7.5% in horses; and 3.7% in humans.
- Human skin contains an average of 40–70 hair follicles and 200–250 sweat glands per square centimeter
- Rabbits>rats>guinea pigs>cats> dogs>pigs and Rhesus monkeys> humans (least permeable skin).
- Hydration is nominally maintained at 10-15 %.
- The hydration to 50% increase the absorption up to 10-fold.

Table 16 Maximal penetration of radiolabeled organophosphorus compound through excised skin from dorsal thorax of various species

Species	Rate ($\mu g/cm^2/min$)
Pig	0.3
Dog	2.7
Monkey	4.2
Goat	4.4
Cat	4.4
Guinea pig	6.0
Rabbit	9.3
Rat	9.3

(From Ref.[115].)

Veterinary liquids praparations for cutaneous application

(Praeparationes liquidae veterinariae ad usum dermicum)

Topical preparations

- **pour on**
  cattle, sheep, pigs, and horses,
- **spot on**
  dogs and cats
- **dip in**
  sheep, cattle

Table 17 Dosage forms and methods of application of topical ectoparasiticide preparations to individual species

Animal species	Dosage form	Method of application
Cattle	Solution	Pour on
	Liquid concentrate[a]	Spray
	Ear tag	Attach to ears
Sheep	Liquid concentrate[a]	Dip, spray
	Solution	Spot on, pour on
Pigs	Solution	Pour on, spot on
	Liquid concentrate[a]	Spray
Horses	Solution	Pour on
	Liquid concentrate[a]	Spray, shampoo
	Lotion	Dab on
Dogs and cats	Solution	Spot on, spray (dogs)
	Collar	Surrounding neck
	Dusting power	Apply to coat
	Liquid concentrate[a]	Sponge on (dogs)
	Shampoo	Wash (dogs)

[a]Liquid concentrates must be appropriately diluted before use on animals.

Dosage forms of Ph. Eur. for veterinary use

Intramammary praparations for veterinary use

(Praeparationes intramammariae ad usum veterinarium)

Intramammary preparations for veterinary use are sterile preparations intended for introduction into the mammary gland via the teat canal. There are two main categories : those intended for administration to lactating animals, and those intended for administration to animals at the end of lactation or to non-lactating animals for the treatment or prevention of infection.

Intramammary preparations for veterinary use are solutions, emulsions or suspensions or semi-solid preparations containing one or more active substances in a suitable vehicle. They may contain excipients such as stabilising, emulsifying, suspending and thickening agents. Suspensions may show a sediment which is readily dispersed on shaking. Emulsions may show evidence of phase separation but are readily redispersed on shaking.

Unless otherwise justified and authorised, intramammary preparations for veterinary use are supplied in containers for use on one occasion only for introduction in a single teat canal of an animal.

If supplied in multidose containers, aqueous preparations contain a suitable antimicrobial preservative at a suitable concentration, except where the preparation itself has adequate antimicrobial properties. Precautions for administration and for storage between administrations must be taken.

During the development of a intramammary preparation for veterinary use, the formulation for which contains an antimicrobial preservative, the effectiveness of the chosen preservative shall be demonstrated to the satisfaction of the competent authority.

Dosage forms of Ph. Eur. for veterinary use

Intramammary praparations for veterinary use

(Praeparationes intramammariae ad usum veterinarium)

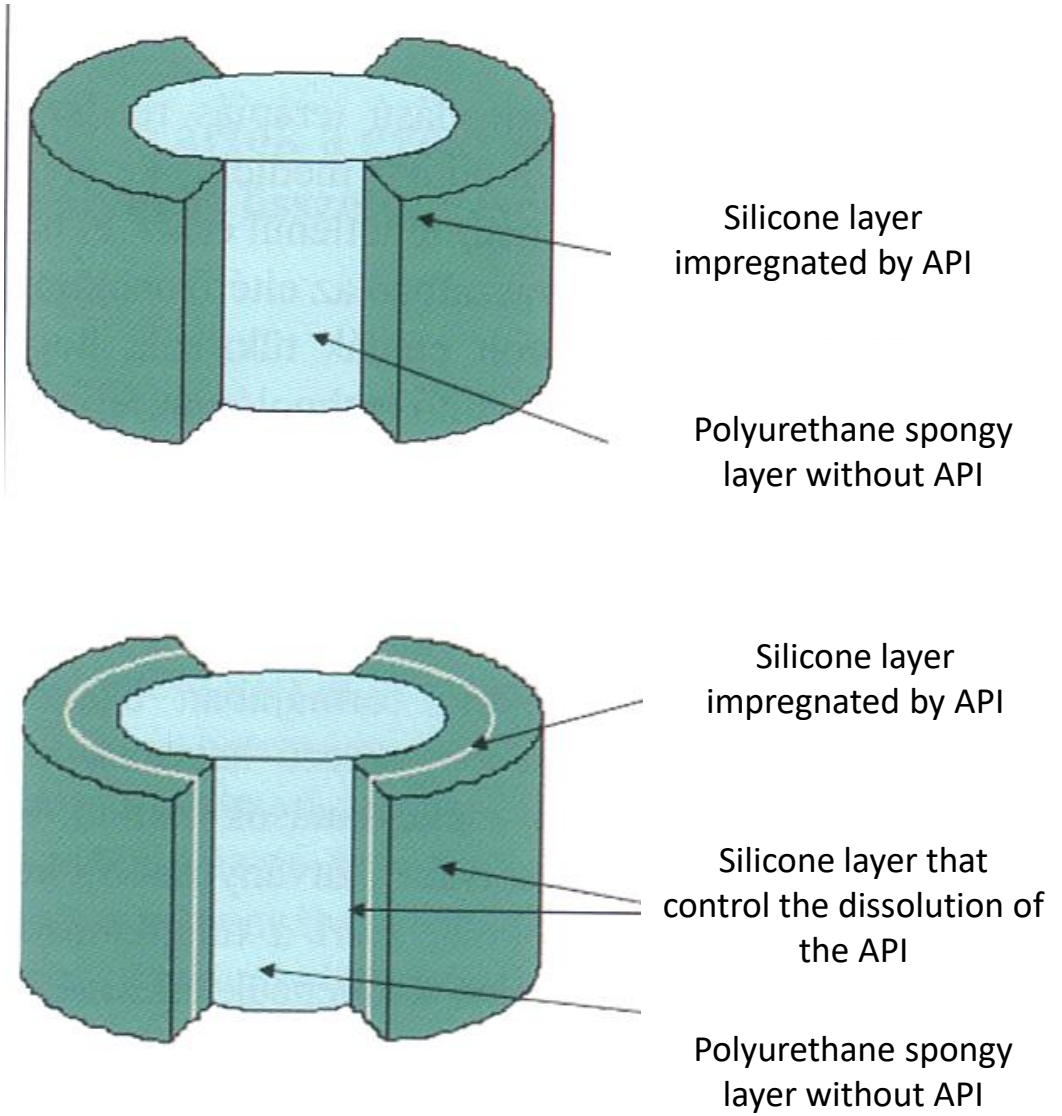
Store in a sterile, airtight, tamper-proof container.

The label states :

- the name of the active substance(s) and the mass or number of International Units of the active substance(s) that may be delivered from the container using normal technique,
- whether the preparation is intended for use in a lactating animal or a non-lactating animal,
- in the case of multidose containers, the name of any added antimicrobial preservative.

- Quick release?
- Short withdrawal period
  (3-4 days: milk; 7 days for slaughter)

Dosage forms of Ph. Eur. for veterinary use



Two types of intravaginal sponge

Formulae Normales Veterinariae IV. (Hungarian)

Pharmacological categories

Groups:

- Metabolism regulators, vitamin, liver protecting agents
- Dermatology, external auditory canal
- Active drugs affecting gastrointestinal function, digestion
- Disinfectant
- Inflammatory and antiinflammatory agents
- Mucolytics, drugs acting on breathe
- Ophtalmicae
- Teat treatment
- Urinary desinfectants
- Various

Which type of dosage form can be recommended for:

- Horses:
  injection,
  sose pipe
  capsule, bolus
- Cattle, sheep:
  drinking water (sol),
  injection,
  capsule, bolus.
- Swine:
  medicated feed,
  injection,
  drinking water (sol),
  ‘electarium’.
- Poultry:
  drinking water (powd.),
  medicated feed
- Pets:
  per os,
  injection.
- Insects:
  syrup,
  smoking strip
- Fish:
  dissolved powder.

Drug sensitivity

Fish:	saponins,
Chicken:	HCH *(hexachlorocyclohexane)*,
Young duck:	furazolidone,
Dog:	streptomycin, HCH, tetramisole, ivermectin,
Horse:	flumequine, Tetramisole, phenylbutazone,
Cat:	paracetamol, primidone, chloramphenicol, HCH,
Swine:	streptomycin, procaine (procain-penicillin!)
Rabit:	gentamycin, linkomycin,
Turkey:	salinomycin
Calf:	nitrofurantoin

Favorite flavors of animals

Flavors that animals prefer include:

- **Dogs** like Beef, Chicken, Cheddar Cheese, Molasses, Peanut Butter, Liver, Raspberry, Strawberry
- **Cats** like Tuna, Chicken, Beef, Cheddar Cheese, Peanut Butter, Liver, Butterscotch.
- **Birds** like Grape, Mandarin Orange, Tutti-Frutti, Molasses, Pina Colada.
- **Horses** like Apple, Creamy Caramel, Molasses, Licorice, Cherry.
- **Rabbits** like Banana
- **Ferrets** like Bubblegum, Molasses.
- **Gerbils** like Mandarin Orange, Tutti-frutti.

Economic considerations (production enhancer)

Most of them are antibacterial agents,

4-6% of them can cause higher body mass and

2-4% better utilization of feedingstuffs:

avoparcin, bacitracin zinc, flavophospholipol, virginiamycin, carbadox, tylosin, monensin

LD_{50} (mg/kg) of monensin differs among species:
horses, 2–3; sheep, 12; pigs, 16; cattle, 22; and chickens, 200.

Economic considerations (preventive mixes; PreMix)

Complex, statistically homogeneous feed supplement powders.

Content:

vitamins, minerals and trace elements,
drugs
growth promotants,
essential amino acids,
enzymes
urea (non-protein N);
flavor.

Premixes must always be diluted to the approved use level, usually parts per million (ppm) [g/tonne (feed) or mg/L (water)], for the animal species.

Are these all important?

The animal healt system is the integral part of a country health care system, because the food-productive animals can seriously threat the public health.

How can we gain information?

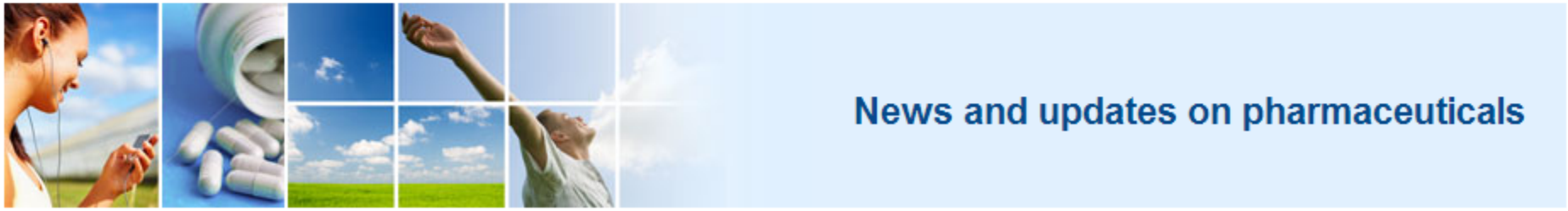
Regulation of medicines

Human medicines

Find regulatory and procedural advice on marketing authorisations, paediatric investigation plans, orphan designations, scientific guidelines, information on advisory services including scientific advice, the micro, small and medium-sized enterprise (SME) office and the innovation task force, inspections and fees.

Veterinary medicines

Find regulatory and procedural advice on marketing authorisations, maximum residue limits, scientific guidelines, information on advisory services including scientific advice and the the micro, small and medium-sized enterprise (SME) office, referrals, inspections and fees.



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Useful links

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU Legislation - Eudralex

The body of European Union legislation in the pharmaceutical sector is compiled in Volume 1 and Volume 5 of the publication "The rules governing medicinal products in the European Union".

- Volume 1 - EU pharmaceutical legislation for medicinal products for human use
- Volume 5 - EU pharmaceutical legislation for medicinal products for veterinary use

The basic legislation is supported by a series of guidelines that are also published in the following volumes of "The rules governing medicinal products in the European Union":

- Volume 2 - Notice to applicants and regulatory guidelines for medicinal products for human use
- Volume 3 - Scientific guidelines for medicinal products for human use
- Volume 4 - Guidelines for good manufacturing practices for medicinal products for human and veterinary use
- Volume 6 - Notice to applicants and regulatory guidelines for medicinal products for veterinary use
- Volume 7 - Scientific guidelines for medicinal products for veterinary use
- Volume 8 - Maximum residue limits
- Volume 9 - Guidelines for pharmacovigilance for medicinal products for human and veterinary use
- Volume 10 - Guidelines for clinical trial

The Rules Governing Medicinal Products in the European Union

Medicinal Products for Human and Veterinary Use

- The pharmaceutical industry of the European Union maintains high standards of Quality Management in the development, manufacture and control of medicinal products. A system of marketing authorisations ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality and efficacy. A system of manufacturing authorisations ensures that all products authorised on the European market are manufactured/ imported only by authorised manufacturers, whose activities are regularly inspected by the competent authorities, using Quality Risk Management principles.
- All Member States and the industry agreed that the GMP requirements applicable to the manufacture of veterinary medicinal products are the same as those applicable to the manufacture of medicinal products for human use.

MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

- **Manufacture of premixes for medicated feedingstuffs**
- *a medicated feedingstuff is any mixture of a veterinary medicinal product or products and feed* or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties as a medicinal product covered by Article 1 (2) of Directive 2001/82/EC;

MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

- Due to the large number of animal species and related pathogenic agents, the variety of products manufactured is very wide and the volume of manufacture is often low; hence, work on a campaign basis is common.

- The environment also must be protected especially when the manufacture involves the use of pathogenic or exotic biological agents and the worker must be particularly well protected when the manufacture involves the use of biological agents pathogenic to man.

MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

- Responsible personnel should be formally trained in some or all of the following fields: bacteriology, biology, biometry, chemistry, immunology, medicine, parasitology, pharmacy, pharmacology, virology and veterinary medicine and should also have an adequate knowledge of environmental protection measures.
- Where relevant, the personnel should be vaccinated and subject to medical examination.
- the absence of direct venting to the outside
- a system for the collection and disinfection of liquid effluents including contaminated condensate from sterilizers, biogenerators, etc. Solid wastes, including animal carcasses, should be disinfected, sterilized or incinerated as appropriate.

- The most complete and concise veterinary product reference available, featuring over 5,000 pharmaceutical, biological, diagnostic, feed medications and parasiticide product monographs categorized by species and treatment type.

http://www.drugs.com/vet/

How is it controlled?

What is the influencing factors of the development?

Regulation

U.S. Code of Federal Regulations (CFR)

Table 3 Product information contained within the CFR

- Name of the drug
- Name of the drug sponsor
- The approved dose, route of administration
- The approved indication (disease and target animal species)
- Withdrawal time and the tolerance (for products to be used in food-producing animals). Information regarding the marker residue and target tissue can be found in the freedom of information summaries that are posted on the CVM website (http://www.fda.gov/cvm/efoi/foidocs.htm)

Regulation

Regulation of new animal drugs

Department of Agriculture,
Center for Veterinary Biologics

Table 5 Technical sections associated with veterinary drug product applications

- Chemistry, manufacturing, and controls section
- Effectiveness
- Target animal safety
- Human food safety
- Environmental impact
- Labeling
- "All other information," which includes, but is not limited to, any information derived from other marketing (domestic or foreign) and favorable and unfavorable reports in the scientific literature

Target animal safety: drug is safe and effective for use as suggested in the proposed labeling

Regulation

Regulation of new animal drugs

Human food safety: the sponsor must demonstrate reasonable certainty of no harm to human health for all drug products intended for use in food-producing animals.

A *residue* is ‘‘any compound present in the edible tissues of the target animal which results from the use of the sponsored compound, including the sponsored compound, its metabolites, and any other substances formed in or on food because of the sponsored compound’s use.

NOEL: a toxicology test, that determines the dose that produces no observed effect.

NOEL=No observed effect level

Regulation

Regulation of new animal drugs

Table 6 Information comprising the HFS technical section

- A toxicological assessment
- The determination of an ADI
- Determination of a safe concentration of drug residues within the target animal species
- Development and validation of an analytical method that serves as the regulatory method for determining the withdrawal time and for assessing whether or not animal-derived products contain residue concentration in excess of the established limit (violative residues of meats and animal-derived food products]
- Establishment of a tolerance
- Establishment of a withdrawal time

Regulation

Regulation of new animal drugs

Human Acceptable Daily Intake (ADI):

$$\text{ADI } (\mu g/kg/day) = [(\text{NOEL } (\mu g/kg))/(\text{Safety Factor } (day^{-1}))]$$

The safety factor acts as a buffer, protecting against errors in interspecies extrapolations or human population predictions.
WHO: a safety factor of 100 units per day is applied when the NOEL is derived from a long-term animal study. It is based on an assumption that humans may be up to 10 times more sensitive than the test animal used and that there may be up to a tenfold range of sensitivity within the human population.
Higher safety factors (e.g., 200, 500, 1000, and 2000) have been applied when incomplete or inadequate data are submitted (e.g., too few animals) or when irreversible or teratogenic and carcinogenic effects have been observed

Regulation

Regulation of new animal drugs

The *safe concentration* is, by definition,

$$Safe\ concentration\left(\frac{\mu g}{g}\right) = \frac{ADI\left(\frac{\mu g}{\frac{kg}{day}}\right) x60\ kg}{grams\ consumed\ /day}$$

the amount of residue that can be eaten in any edible tissue each day for an entire lifetime without exposing the consumer to residues in excess of the ADI.

To estimate the safe concentration, FDA considers the ADI, the weight in kilogram of an average adult human (60 kg), and the amount of the product that may be consumed in grams per day.

Regulation

Pharmacovigilance

Similarly to human therapy.

It includes the adverse drug rection appearing in case of the owner / the farmer.

- Side effects (prescribed application?)
- Effect (lack of effect? Why?)
- Side effects in human body
- Residue problems (storage)
- Environmental Pollution Options (EPO)

Thank you for your attention