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MedPlants 4Vet

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Funded by the European Union

ASSESSMENT OF THE SAFETY FOR A HERBAL VETERINARY MEDICINAL PRODUCT

MedPlant4Vet – Training course
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1- Background - Definitions

Background – Definition of VMP

- any substance or combination of substances presented as having properties for treating or preventing disease in animals;

- any substance or combination of substances that may be used in, or administered to, animals with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action;

- or to be used with a view of making a medical diagnosis;

- or to be used for euthanasia of animals

→ If a herbal product / plant extract / EO with therapeutic claim
→ = veterinary medicine

The life of a VMP

Research & Development

Authorities

Manufacturing & Marketing

Prescription & Use

benefit/risk balance

MRL establishment

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Marketing authorisation

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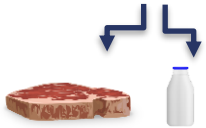
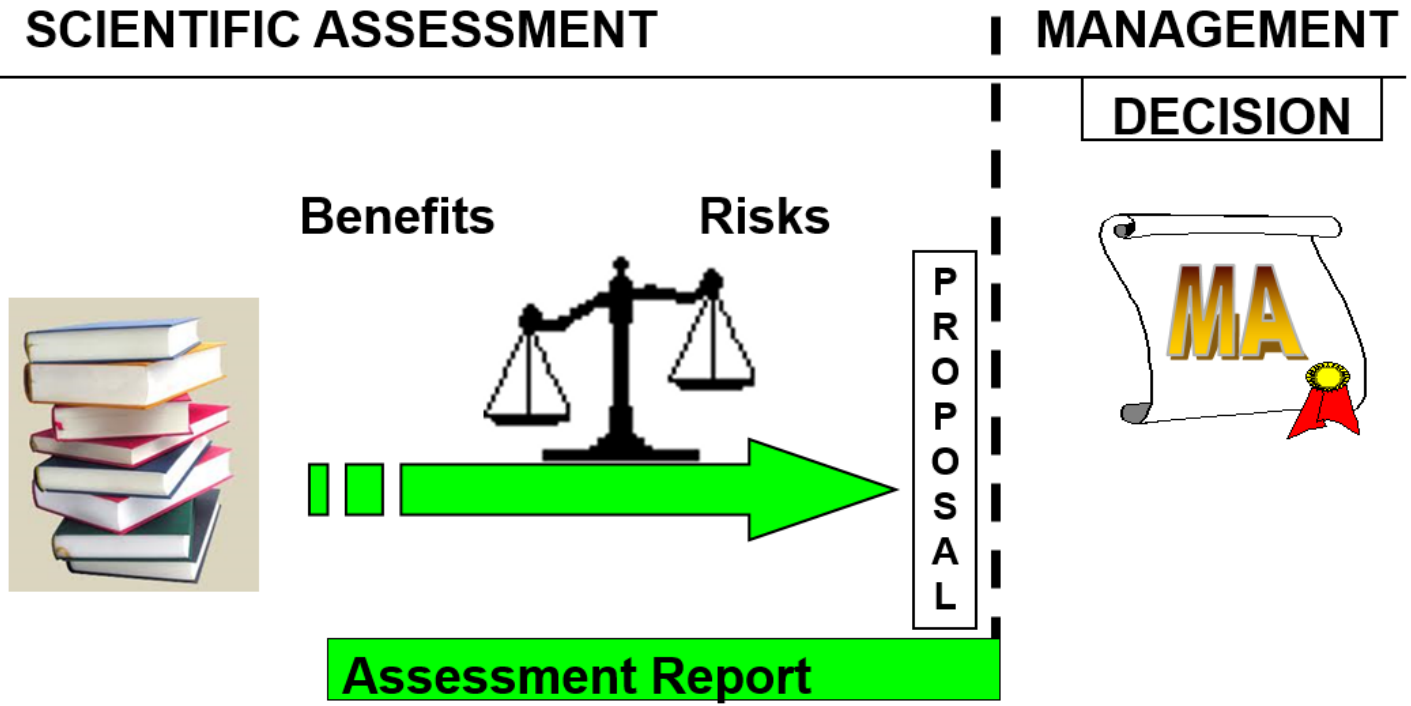


Consumption & Control – Post MA

Assessment for Marketing authorisation



Dossier of marketed autorisation of pharmaceutical VMP
Regulation (EU) 2019/6 and Commission delegated regulation (EU) 2021/805

Part 1

- Summary of the dossier

Part 2 : Quality documentation

- A - Product description
- B – Description of the manufactoring method
- C – Production and control of starting material
- D – Control tests carried out on isolated intermediates during the manufacturing process
- E – Control tests on the finished product
- F – Stability tests
- G – Other information

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Part 3 : Safety documentation

- A – Safety tests
  - Toxicology
  - User safety
  - Environmental risk assessment
- B – Residues tests

Part 4 : Efficacy documentation

- A - Pre-clinical studies
  - Pharmacology
  - Resistance
  - Tolerance
- B – Clinical trials

2- Safety part

Part 3.A.3. Toxicological tests

Dossier: Part 3.A.1

Single dose toxicity

Prediction of a) the possible effects of acute overdose in the target species;
b) the possible effects of accidental administration to humans;
c) the doses which may usefully be employed in the repeat dose studies.

Repeat dose toxicity

- to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how those changes are related to dosage.

Reproductive toxicity including developmental toxicity

- study of the effects on reproduction;
- study of developmental toxicity (including teratogenicity)

Genotoxicity

- standard battery of genotoxicity tests in accordance with standard tests based on established guidance (including VICH GL23 and OECD tests) shall be carried out on the active substance(s).

Carcinogenicity

- Requirement of studies shall take into account the results of genotoxicity tests, structure-activity relationships and the findings in repeat dose toxicity tests that may demonstrate the potential for hyper-/neo-plastic changes.

- Carcinogenicity testing shall be conducted according to standard tests based on established guidance (including VICH GL28 and OECD tests).

Other requirements

- **Special studies**

For particular groups of substances or if the effects observed during repeated dose studies in animals include changes indicative of, for example, immunotoxicity, neurotoxicity or endocrine dysfunction, further testing shall be required.

For products for which there may be exposure to skin and eyes, irritation and sensitisation studies shall be provided. Those studies shall be conducted with the final formulation.

- **Observations in humans**

Information shall be provided showing whether the pharmacologically active substances of the veterinary medicinal product are used as medicinal products in human therapy

- **Development of resistance and related risk in humans**

WHEN PERFORM TOXICOLOGICAL STUDIES ?

Studies are required for all NEW substance(s) in a veterinary medicinal product.

For VMP intended to be used in food producing species, all substances must have a MRL status.

Consequently, toxicological profile of these substances are already assessed in the MRL dossier. There is no need to perform new toxicological tests.

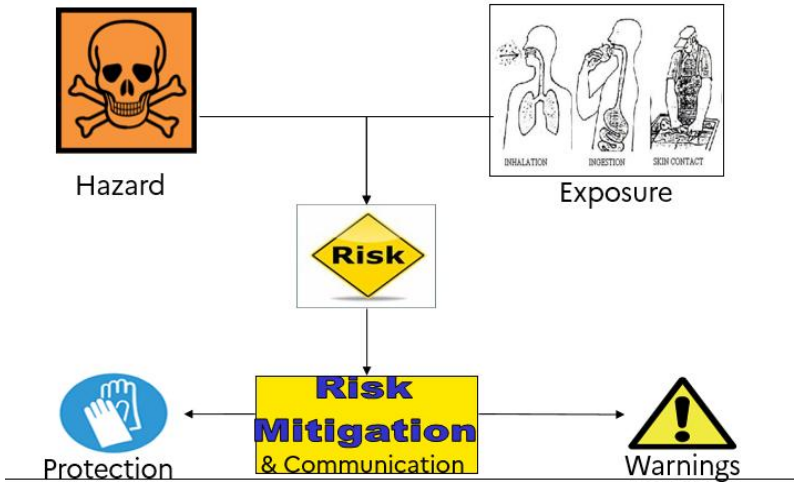
In the same way, most of substances used in VMP for pet animals are also used in food producing species.

Toxicological data from MRL dossier are valuable also for VMP for pet animals.

This is in line with 3Rs approach.

Part 3.A.5. USER SAFETY

Principles of the user risk assessment



Two CVMP guidelines

- Guideline on user safety for pharmaceutical veterinary medicinal products
- Guideline on user safety of topically administered veterinary medicinal products

Hazard identiication: inherent toxicity of the active substance(s)

- Part A.3.A Toxicological tests: systemic and local effects

Exposure assessment

- The VMP: relevant physico-chemical characteristics ; the presentation (quantity available to the user, packaging); the method of use, including the route of administration and any dosing equipment to be used.
- Tasks and situations that lead to exposure

Exposure scenario

- Who? … the type of user,
- How?... the routes of exposure,
- What? … the components of a product to which the user is exposed,
- When/if? … the probability of exposure,
- How much? How often? … the rate, extent, duration, interval, and frequency of exposure.

Risk characterisation

- Qualitative (no threshold): *e.g.* hypersensitivity, ocular/skin irritation…
- Quantitative (= Margin of Exposure)

$$\frac{NOAEL}{Exposure}$$

MOE > 100 ⟹ No risk

MOE < 100 ⟹ RISK ⟹ Warnings/recommendations

Risk management / communication

- Communicated via the SPC and package leaflet and should inform the user about the following aspects:

A. The concerned risk.

B. What exposure must be avoided to minimize the concerned risk.

C. How to avoid that exposure.

D. What to do in the event of exposure (if relevant).

Part 4.A.4. Tolerance

Tolerance

Legal framework – Regulation 2019/6

II.4A4. Tolerance in the target animal species

"The local and systemic tolerance of the veterinary medicinal product shall be investigated in the target animal species. The purpose of target animal safety studies is to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration. This may be achieved by increasing the dose and/or the duration of treatment. The study report(s) shall contain details of all expected pharmacological effects and all adverse reactions. The conduct of target animal safety studies shall be in accordance with the international guidelines of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products ("VICH") and relevant guideline(s) published by the Agency. Other pre-clinical studies, including studies provided in part 3, and clinical trials, along with relevant information from the published literature, may also provide information on safety in the target species. Studies on developmental toxicity performed in the target animal species shall be included here, and a summary shall be provided in Part 3 of the dossier."

Tolerance

Guidelines

General reference guideline:

- **VICH GL 43** «Target Animal Safety for Veterinary Pharmaceutical Products »

Specific guidelines

- For VMPs intended for use in farmed finfish
- For anti-cancer VMPs
- For performance enhancers
- For VMPs controlling varroa destructor in bees
- For VMPs for zootechnical purposes

Multidisciplinary guidelines

- For fixed combination products
- For VMPs intended for limited markets: - *Under Art 23 of Regulation (EU) 2019/6*
  - Not eligible to autorisation under Art 23

Tolerance - VICH GL43

VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH GL 43 (TARGET ANIMAL SAFETY) - PHARMACEUTICALS
July 2008
For implementation at Step 7

TARGET ANIMAL SAFETY FOR VETERINARY PHARMACEUTICAL PRODUCTS

Adopted at Step 7 of the VICH Process
by the VICH Steering Committee
in July 2008
for implementation in July 2009

THIS GUIDELINE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND HAS BEEN SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT IS RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

- This guideline concerns bovine, ovine, cats, dogs, porcine, equine and poultry (chickens and turkeys)).
- For minor species or fishes, one can use other suitable guidelines. These subjects should be considered on a case-by-case basis

Tolerance - VICH GL43

Preamble for all pre-clinical studies (including TAS): animal welfare regulations should generally be abided by, and husbandry of the animals is expected to comply with Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes.

Purpose of a tolerance study: establishment of a safety margin of a VMP in the target species.

Basic requirements for a well conducted tolerance study

- Principles of GLP.
- **Healthy animals** (to differentiate between disease-related and VMP-related effects) (n ≥ 8/group)
- The tolerance should be assessed for all claimed ages.
- Control and treated animals should be managed identically (same prophylactic treatments)
- No concurrent therapy (except prophylactic treatments)
- **Final formulation intended for marketing.**
- Overdoses (1, 3, 5X), longer duration than claimed.

Tolerance - VICH GL43

Assessed variables

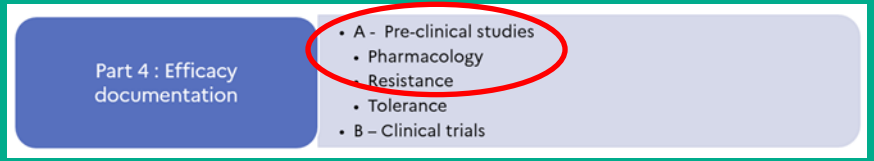
- Physical examinations by a qualified person, at several time points during the study (always at the beginning and the end of the study)
- General health, behaviour: once a week, 7 days/7.
- Food and water consumption.
- Body weight (at the beginning, and several other appropriate intervals).
- Haematological/biochemical parameters and urinalysis
- Necropsy and histopathology examinations

Tolerance - VICH GL43

Other designs

- Injection Site Safety Studies : claimed max volume, claimed duration, vehicle (same volume)
- Administration Site Safety Studies for Dermally Applied Topical Product : claimed dosage. Oral dosing should be of interest.
- Reproductive safety studies (breeding animals): 3X claimed dose, on males and females.
- Mammary Gland Safety Studies

3- Preclinical part



Regulation

European Regulations

(UE) 2019/6 of 11/12/2018

VICH Guidelines

VICH GL 52 (bioequivalence)

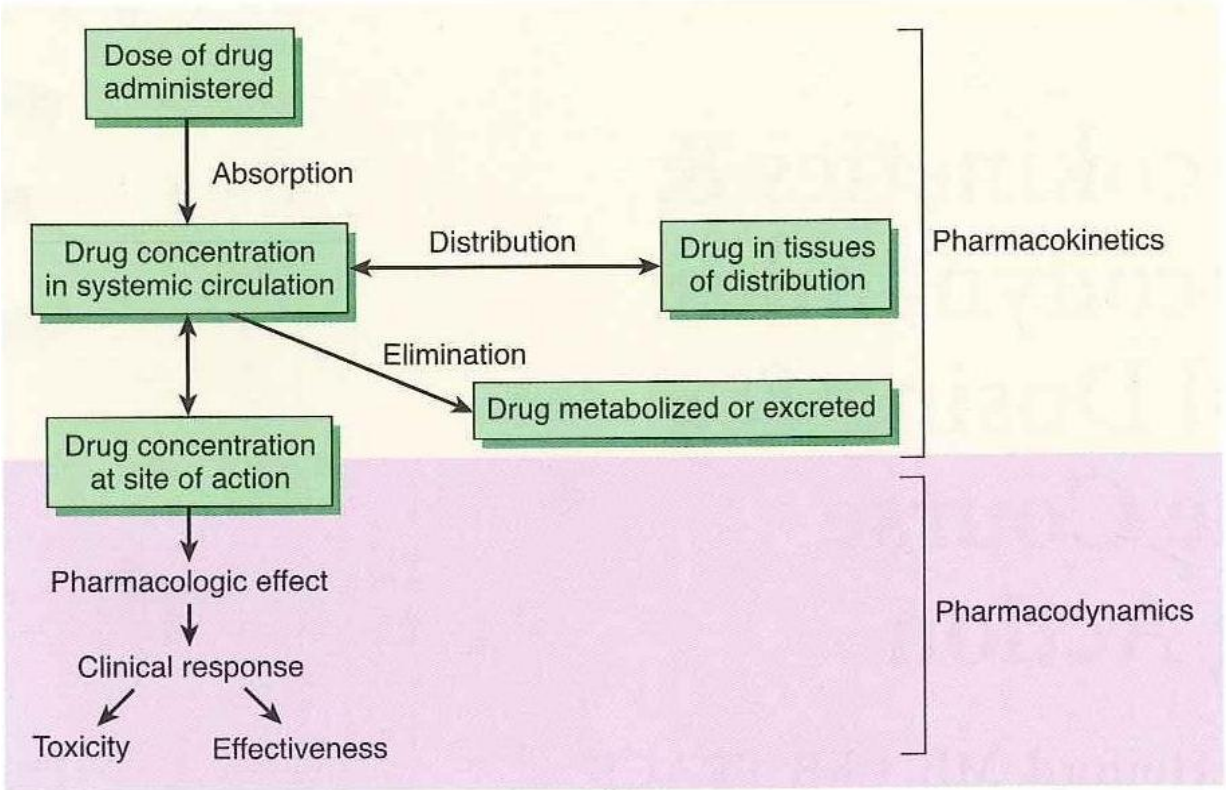
CVMP Guidelines

EMA/CVMP/016/2000 (bioequivalence)
EMA/CVMP/133/1999 (PK)
EMA/CVMP/344/1999 (intra-mammary)
EMA/CVMP/EWP/005/2000 (APE)
EMA/CVMP/627/2001-Rev.1 (antimicrobial)

Pharmacology

Pharmacology

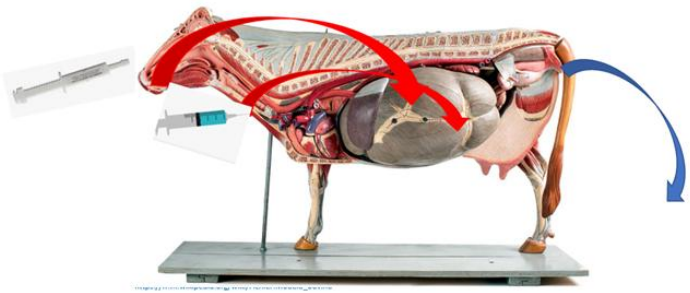
Overview of process



Pharmacology

- Drug with marketing authorisation (MA)

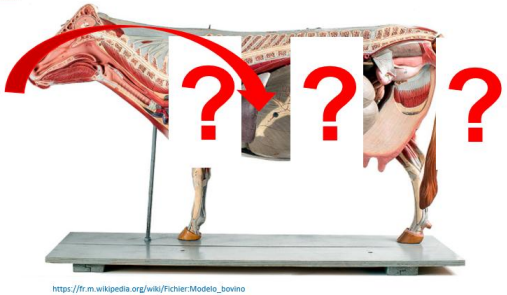
One Molecule



Absorption Distribution Metabolisation Elimination

- Herbal product

100-150 molecules



https://fr.m.wikipedia.org/wiki/Fichier:Modelo_bovino

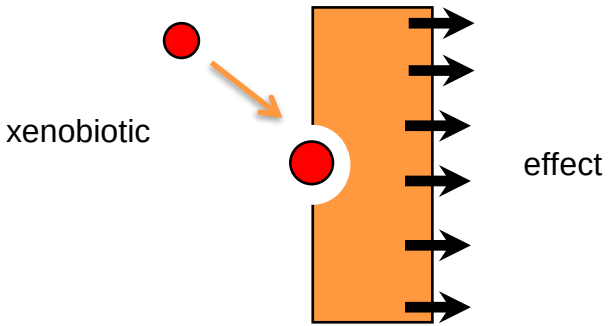
Absorption Distribution Metabolisation Elimination

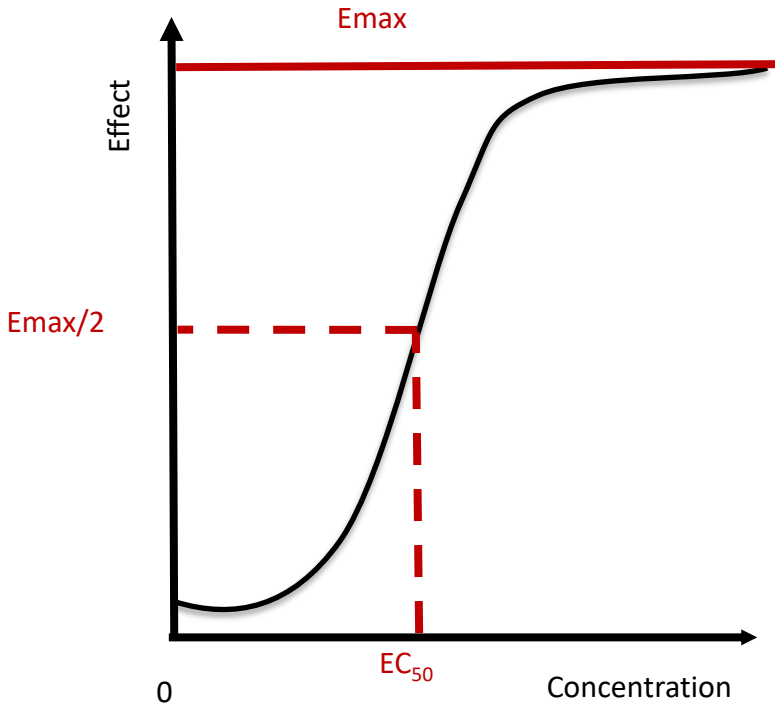
Part 4.A.1.1- Pharmacodynamics

Pharmacodynamics

Pharmacodynamics is the study of how a drug affects an organism.

Study of the effects according to active substances concentration.





Pharmacodynamics

Choice of the active substance

Fundamental importance in clarifying the mechanisms

Efficacy and toxicity

- ❑ Pharmacological class/ therapeutic group
- ❑ Mechanism of action / mode of action
- ❑ Secondary pharmacological effects (adverse reactions)
- ❑ Efficacy concentration
  - Antiparasitic substances : lethal concentration
  - Antimicrobial substances : minimal inhibitrice concentration
  - Others substances: effect concentrations
- ❑ Justification of fixed combination

in vitro model
Published papers
in vivo studies

Dossier: Part 4.A.1.1

Part 4.A.1.2 - Pharmacokinetics

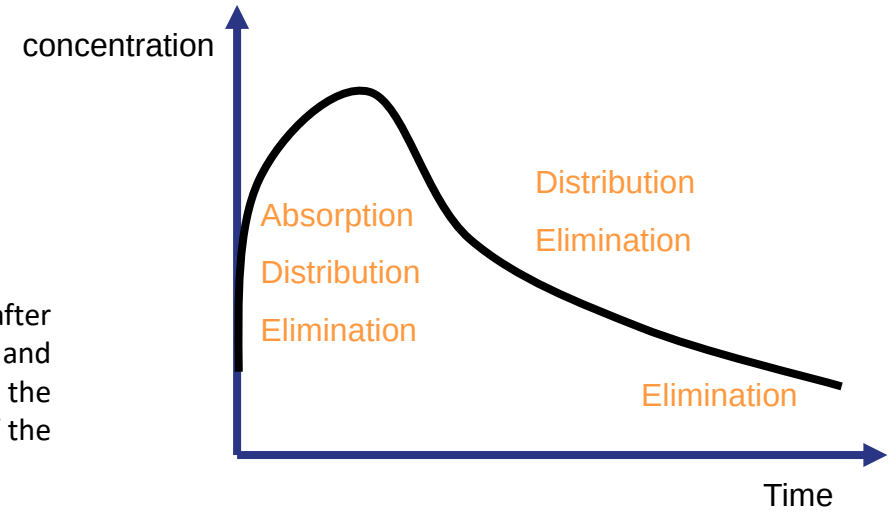
Pharmacokinetics

Support studies on clinical efficacy and safety.

Study of the time course of substance absorption, distribution, metabolism and excretion (ADME)

Pharmacokinetics describes how the body affects a specific drug after administration. This occurs through the mechanisms of absorption and distribution, as well as the metabolic changes of the substance in the body, and the effects and routes of excretion of the metabolites of the drug.

How is such a profile determined?



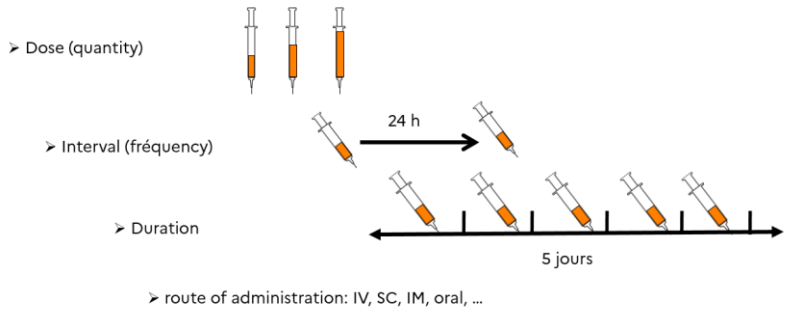
Plasmatic pharmacokinetic profile

Pharmacokinetics: *in vivo* study

The plasma kinetics in the target species following administration of the final formulation

- Target animal species (healthy)
- Final formulation of the VMP
- All recommended doses (administration route iv)
- Sampling blood
- Validated analytical method
- GLP
- PK calculations with software

The dosage regimen: several factors



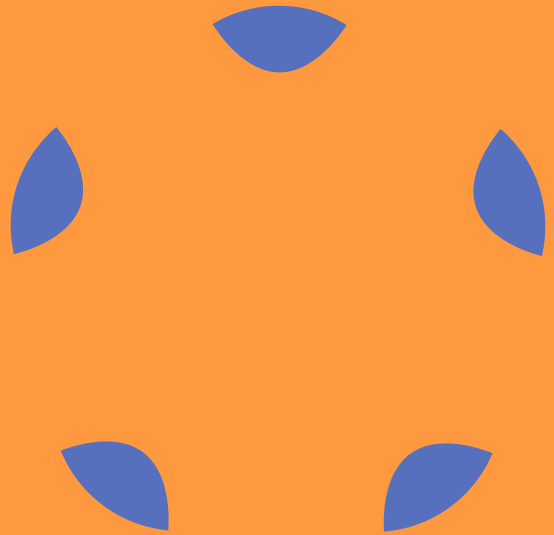
Pharmacokinetics

1. **ADME, plasmatic profile (AUC, Cmax, Tmax, Cl)**
2. **Bioavailability study (F)**
3. **Plasma protein binding (fu)**
4. Gender influence
5. Food effect (for oral route)
6. Linearity according to the dose
7. Accumulation (if repeated administration)
8. Stereoselectivity
9. Impact of modification of formulation => bio-equivalence

Choice of the dosage regimen

Published papers
in vivo studies with healthy animals
Modelling

PK/PD analysis

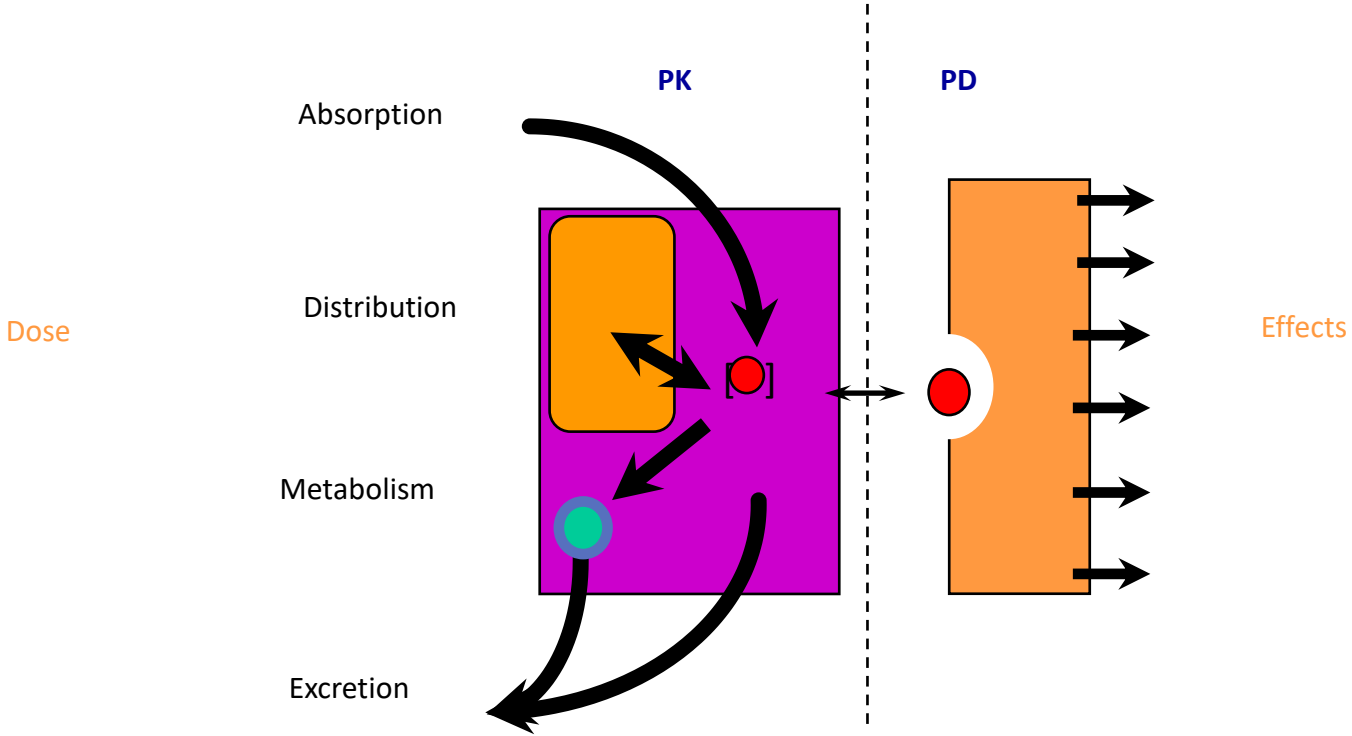


What is PK/PD analysis?

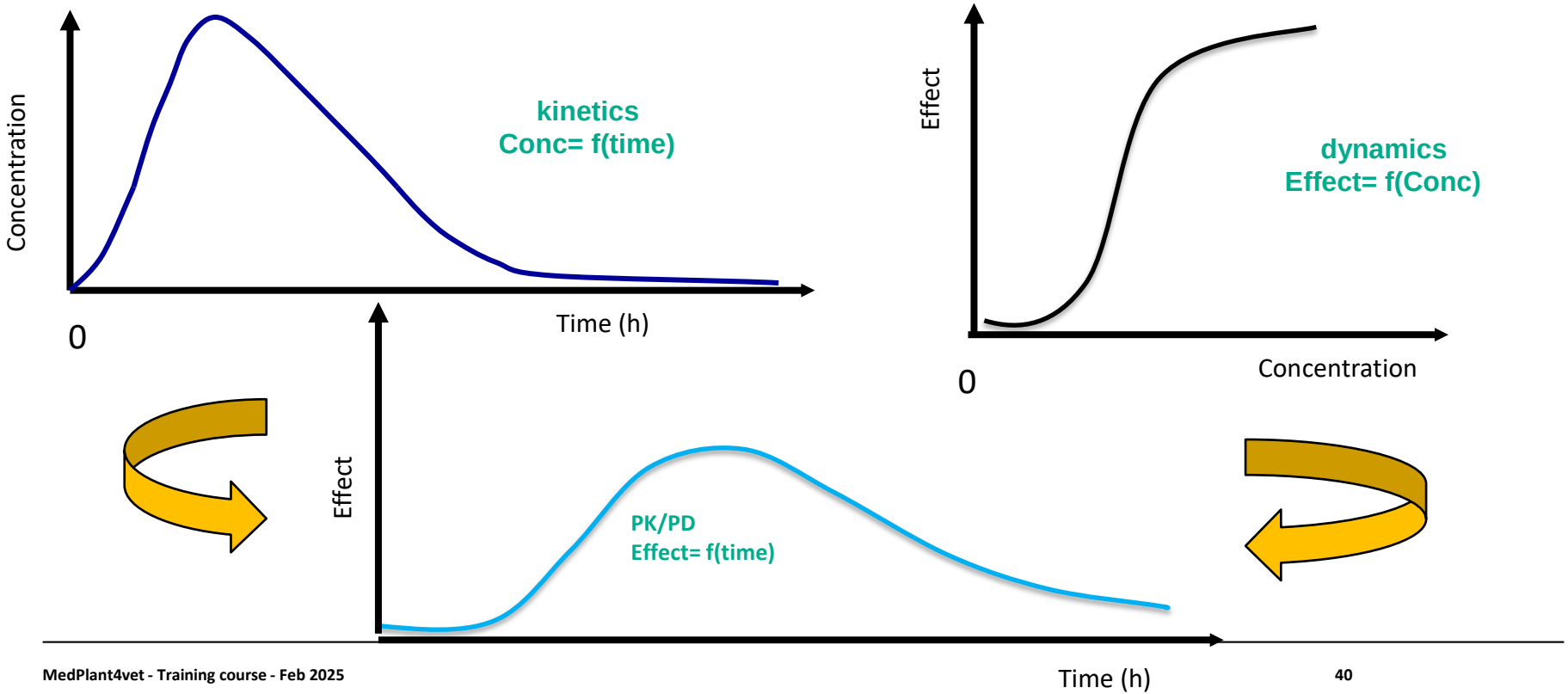
- **PK/PD analysis** is a scientific tool for quantifying *in vivo* the key PD parameters of a drug, which allows to predict the time course of drug effects under given physiological and pathological conditions (intensity & duration)

↳ It is an alternative to dose-determination studies for determining an optimal dose regimen.

Pharmacokinetics and Pharmacodynamics



The PK/PD analysis : study of the effect over the time



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Part 3 : Safety documentation

- A – Safety tests
  - Toxicology
  - User safety
  - Environmental risk assessment
- B – Residues tests

Part 4 : Efficacy documentation

- A - Pre-clinical studies
  - Pharmacology
  - Resistance
  - Tolerance
- B – Clinical trials

Thank you for your attention