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Modalities (authorisation process, surveillance, distribution, control)

Marketing authorisation and assessment procedures

Workshop for OIE national Focal Points for Veterinary Products
23 – 26 November 2010, Johannesbourg, South Africa

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Content

- Marketing Authorisation procedure General scheme
- Marketing authorisation dossier
  - Pharmaceuticals
  - Immunolgicals
- Minor species registration

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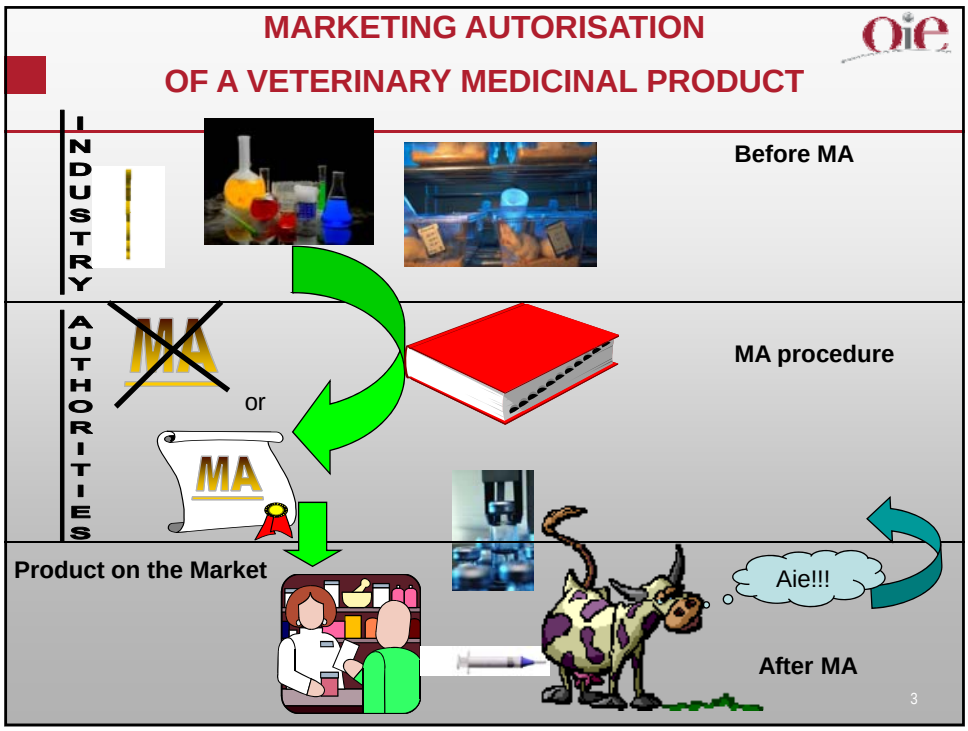
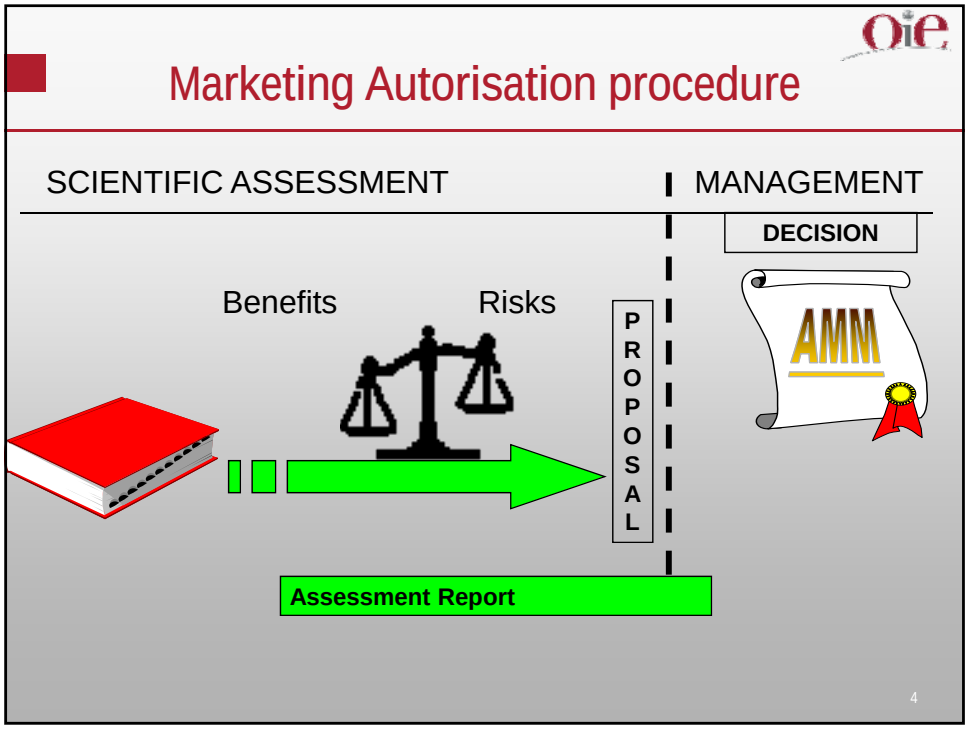
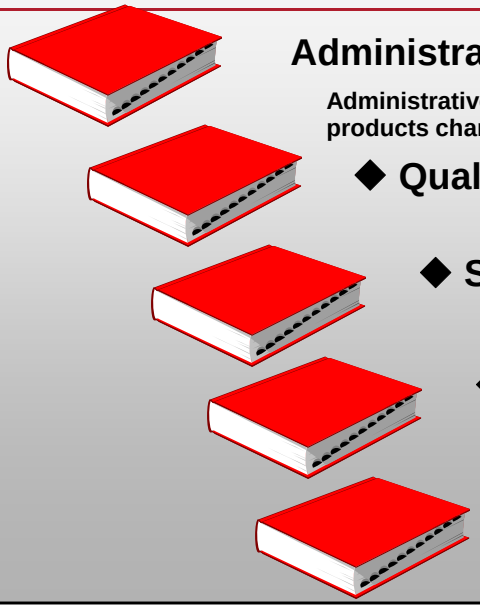

MARKETING AUTORISATION
OF A VETERINARY MEDICINAL PRODUCT
INDUSTRY
AUTHORITIES
Before MA
MA procedure
MA
or
MA
Product on the Market
Aie!!!
After MA
3


Marketing Autorisation procedure
SCIENTIFIC ASSESSMENT
MANAGEMENT
DECISION
Benefits
Risks
PROPOSAL
AMM
Assessment Report
4

Marketing autorisation dossier



Administrative part

Administrative informations, Summary of products characteristics Labelling

- **Quality part**
- **Safety part**
- **Residue part**
- **Efficacy part**

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MA dossier

- Each part contains:
  - Expertise
  - Synthesis of the documentation
  - Documentation

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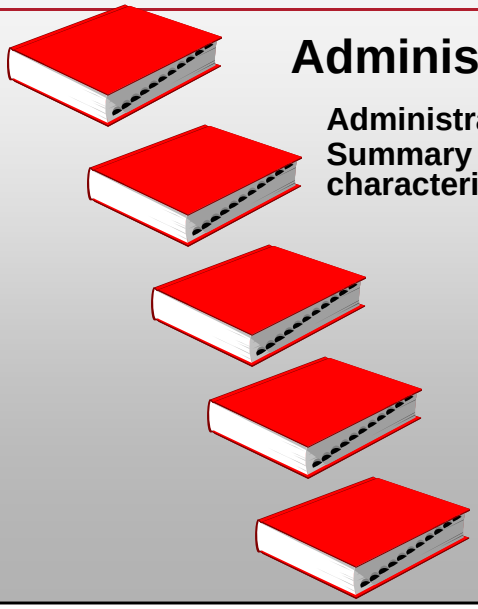
Marketing autorisation dossier



Administrative part

Administrative informations, Summary of products characteristics Labelling

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SPC: Summary of product characteristics

THE CONTENT OF THE SPC MUST BE JUSTIFIED IN THE DOSSIER

THE SPC IS :

- PART OF THE ASSESSMENT REPORT
- PART OF THE MARKETING AUTHORISATION
- A BASIS FOR THE LABELLING ?
- A BASIS FOR THE CONTROL OF ADVERTISING

A

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SPC: Summary of product characteristics

1) name of the veterinary medicinal product
2) qualitative and quantitative composition
3) pharmaceutical form;
4) clinical particulars:
   - 4.1. target species,
   - 4.2. indications for use, specifying the target species,
   - 4.3. contra-indications,
   - 4.4. special warnings for each target species,
   - 4.5. special precautions for use,
   - 4.6. adverse reactions (frequency and seriousness),
   - 4.7. use during pregnancy, lactation or lay,
   - 4.8. interaction with other medicinal products and other forms of interaction,
   - 4.9. amounts to be administered and administration route,
   - 4.10. overdose (symptoms, emergency procedures, antidotes), if necessary,
   - 4.11. withdrawal periods for the various foodstuffs

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SPC: Summary of product characteristics

5) pharmacological properties:
   - 5.1. pharmacodynamic properties,
   - 5.2. pharmacokinetic particulars;
6) pharmaceutical particulars:
   - 6.1. list of excipients,
   - 6.2. major incompatibilities,
   - 6.3. shelf life, when necessary after reconstitution of the medicinal product or when the immediate packaging is opened for the first time,
   - 6.4. special precautions for storage,
   - 6.5. nature and composition of immediate packaging,
   - 6.6. special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products, if appropriate;
7) marketing authorisation holder;
8) marketing authorisation number(s);
9) date of the first authorisation

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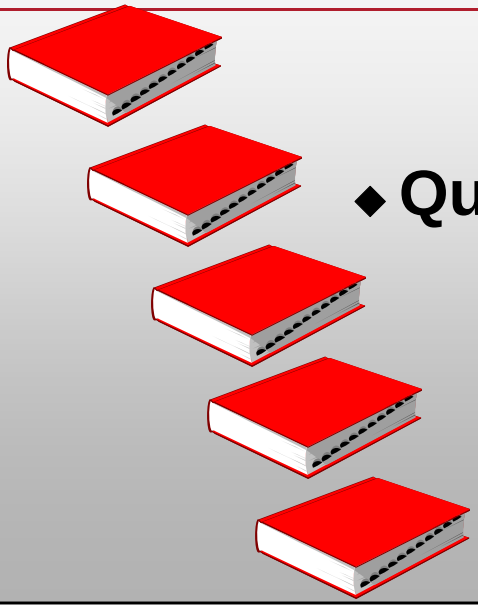
Marketing autorisation dossier



- Quality part

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Regulatory Requirements

- **Guidelines**
  - ➔ VICH : harmonized regulatory requirements European Union, USA and Japan

    GLs 1, 2, 3, 4, 5, 8, 10, 11, 17, 18, 39, 40, 45
  - ➔ EMA : harmonized regulatory requirements European Union
- **Pharmacopoeia :**
  - ➔ European Pharmacopoeia
  - ➔Pharmacopoeia of a Member State: French Pharmacopoeia, British Pharmacopoeia...
  - ➔ USP

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Part II Framework

- A – Qualitative and Quantitative Particulars of the Constituents
- B – Description of the Manufacturing Method
- C – Control of Starting Materials
- D – Specific Measures Concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies (TSE)
- E – Control Tests carried out at Intermediate stage of the Manufacturing process
- F – Tests on the Finished Product
- G – Stability Test
- Q – Other information

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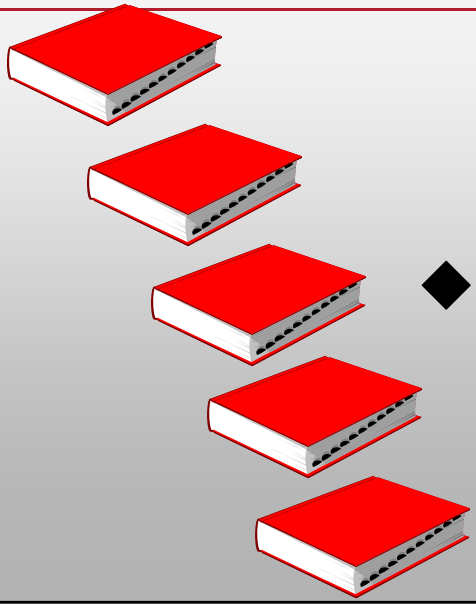
Marketing autorisation dossier



- Safety part

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Safety Part

Toxicological data	Pharmacological data
Single dose toxicity	Pharmacodynamics
Repeated dose toxicity	Pharmacokinetics
Tolerance in the target species of animal	
Reproductive toxicity including developmental toxicity	
Mutagenicity	
Carcinogenicity	

Other requirements Immunotoxicity Neurotoxicity Microbiological properties of residues Potential effects on the micro-organisms used in the industrial processing of foodstuffs Observations in humans

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Risk analysis for Veterinary Medicinal Products

- RISKS:
  - For the animal
  - For the user
  - For the environment
  - For the consumer

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Risk for the animal

- No formalized risk analysis process
  - Tolerance study once and 3 times the dose for the target species
  - Local tolerance study
  - Risk management measures:
    - No Autorisation of the veterinary medicinal products if poorly tolerated
    - Limitation of the injection volume
    - Information given on SPC, labelling…

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Risk analysis for Veterinary Medicinal Products

- RISKS:
  - For the animal
  - For the user
  - For the environment
  - For the consumer

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User safety

- European Guideline EMEA/CVMP/543/03-Final
- Risk assessment
  - Exposure assessment
  - Hazard Identification
  - Hazard characterization
  - Risk characterization
- Risk management
- Risk communication

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User Safety

- Exposure assessment
  - Description of the veterinary medicinal products
  - Tasks and situations that may lead to exposure
  - Exposure scenarios
    - Type of user
    - Route of exposure
    - The components of a product to which the user is exposed
    - Likelihood of exposure
    - Rate, duration, interval and frequency of exposure
- Hazard identification and hazard characterization
  - Toxicity studies according to exposure route
    - Examples
      - Eye irritation for ocular exposure route
      - Accidental Injection : acute toxicity by parenteral
- Risk characterization
  - Qualitative and quantitative risk characterisation
    - No Effect Level (NOEL) plus safety factor (10 extrapolation men-animal; 10 inter species variation).

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User safety

- Risk management
  - Professional users
  - Non-professional users
  - Risk control options
- Risk communication
  - SPC, labelling

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Risk analysis for Veterinary Medicinal Products

- RISKS:
  - For the animal
  - For the user
  - For the environment
  - For the consumer

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ENVIRONMENTAL RISK ASSESSMENT OF VMP

Step I (Guideline VICH GL6)

Some products are exempted from a phase II assessment (decision-tree analysis):

- ➔ Treatment of a small number of animals
- ➔ Companion animals
- ➔ Inert substances (homeopathy, mineral, plants)
- ➔ Foreseeable concentrations are not high

This corresponds to an exposure assessment step.

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ENVIRONMENTAL RISK ASSESSMENT OF VMP

Step II (Guideline VICH GL38)

- Phase II
  Risk assessment using a “tiered” approach
  - Exposure refinement
  - Hazard Identification
  - Hazard characterization
  - Risk characterization
- Risk management
- Risk communication

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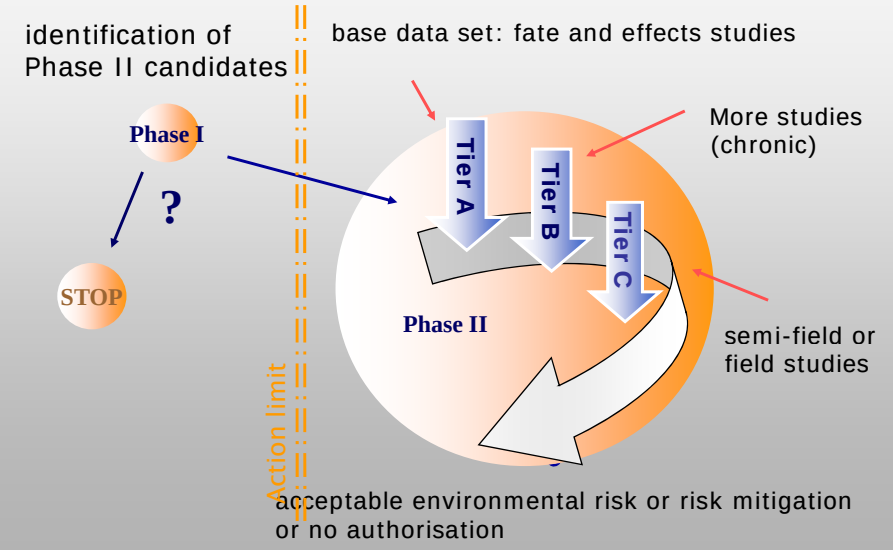
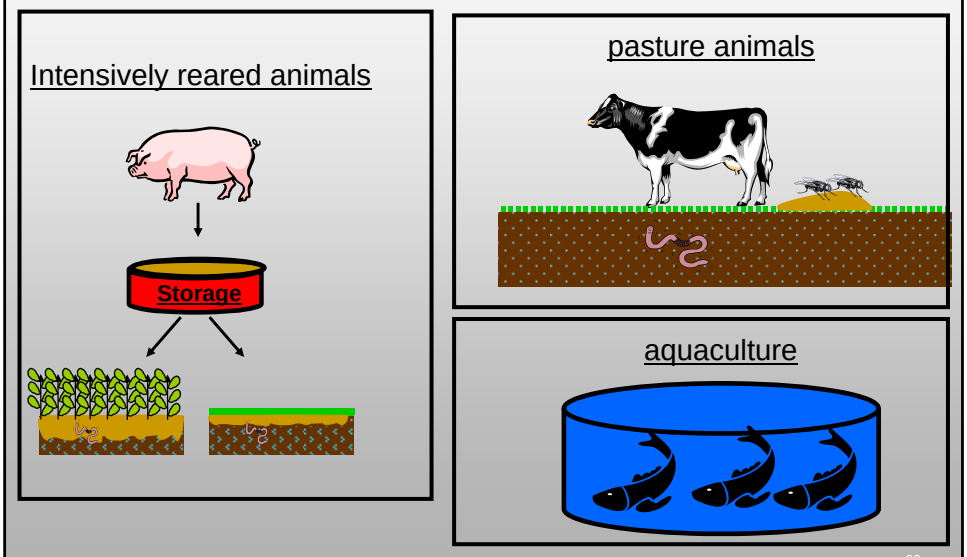
The VICH approach: two-phased, logically tiered



Based on PEC: Predicted Environmental Concentration, Trigger value 100 µg/kg

Branches identified in VICH



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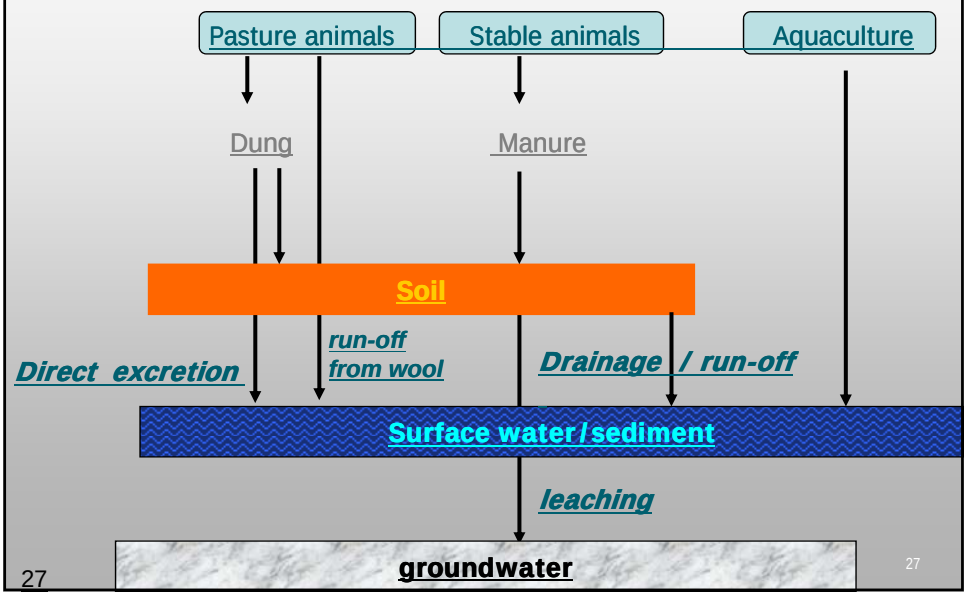
Exposure route of VMPs



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Risk mitigation – recommendations in VICH

If the use of a product results in an unacceptable risk for the environment, then mitigation measures should be proposed by the applicant in order to reduce the risk to an acceptable level

To be effective the risk mitigation measure should:

- Mitigate exposure of the VMP to the environment;
- Be in line with agricultural practise;
- The effect of the proposed risk mitigation measure should be demonstrated by scientific means.

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Risk analysis for Veterinary Medicinal Products

- RISKS:
  - For the animal
  - For the user
  - For the environment
  - For the consumer

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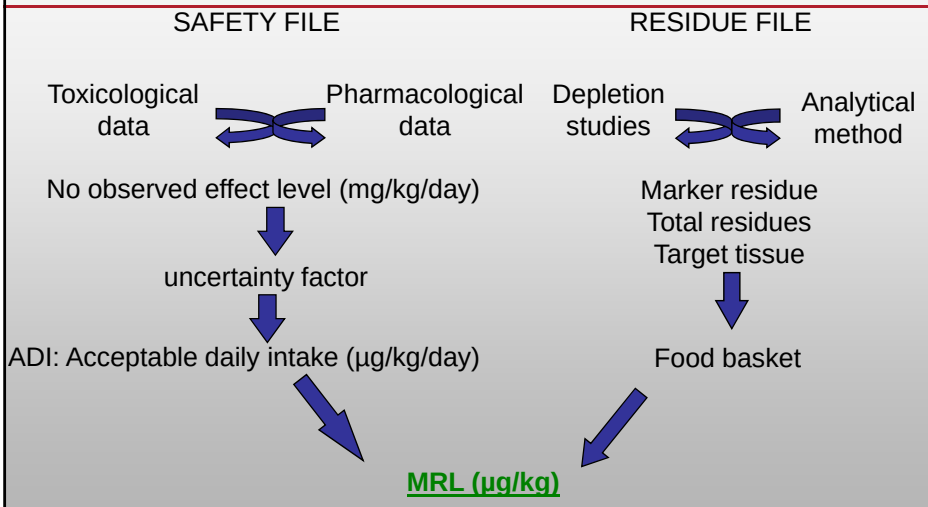
How a MRL (Maximum residue limit) is established ?



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Principles of MRL risk assessment

- **it is assumed that the average person consumes, on a daily basis, 500 g of meat (made up of 300 g of muscle, 100 g of liver, 50 g of kidney and 50 g of fat) together with 1.5 litres of milk and 100 g of eggs or egg products.**
- **All these products are supposed contaminated by residues**

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Outcome:

=> substances with final MRL

=> substances for which it is not necessary to establish a MRL (absence of public health risks)

=> substances with provisional MRL

=> substances for which no MRL can be establish (hazard to the health of the consumer whatever the concentration)

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MRLs established

Meat & offal

Milk

Egg

Honey

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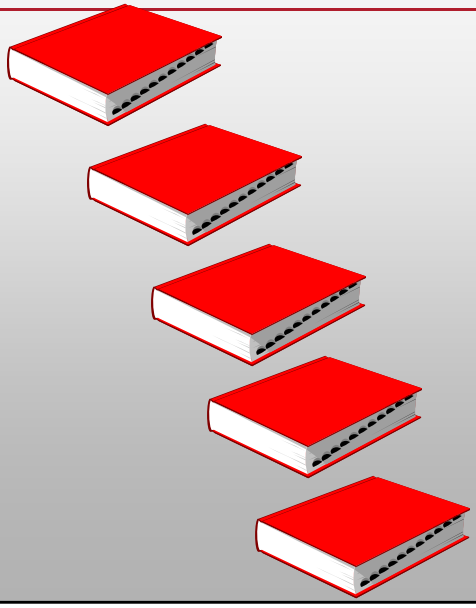
Marketing autorisation dossier



- Residue part

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Goals

To determine withdrawal periods:
The period necessary between the last administration of the veterinary medicinal product to animals, under normal conditions of use, and the production of foodstuffs from such animals, in order to protect public health by ensuring that such foodstuffs do not contain residues in quantities in excess of the maximum residue limits for active substances

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Definitions

A withdrawal period is established for:

- **a medicinal product**
- **an animal species**
- **a foodstuff of animal origin (meat & offal, milk, egg, honey)**

Based on established MRLs:

From a depletion study

With a validated analytical method

By statistical or alternative approach

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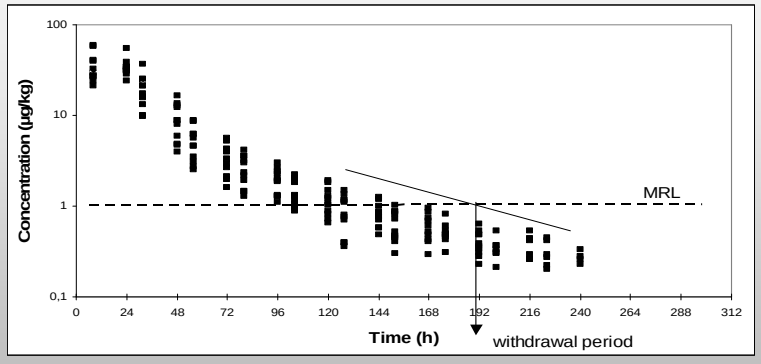
Depletion study



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Analytical method

A Validated analytical method should be provided

- **Not a routine analytical method**
- **Physicochemical method**
- **Concentration range 1/2xMRL to 2xMRL**
- **Accuracy & precision**
- **Quantification and detection limits**
- **Stability of marker residue in foodstuff**

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Several withdrawal periods for one VMP- SPC 4.11

A VMP indicated for cattle
« **meat & offal** » withdrawal period
« **milk** » withdrawal period

A VMP indicated for poultry
« **meat & offal** » withdrawal period
« **egg** » withdrawal period

A VMP indicated for bovine & porcine species
Cattle:
« **meat & offal** » withdrawal period
« **milk** » withdrawal period
Pig:
« **meat & offal** » withdrawal period

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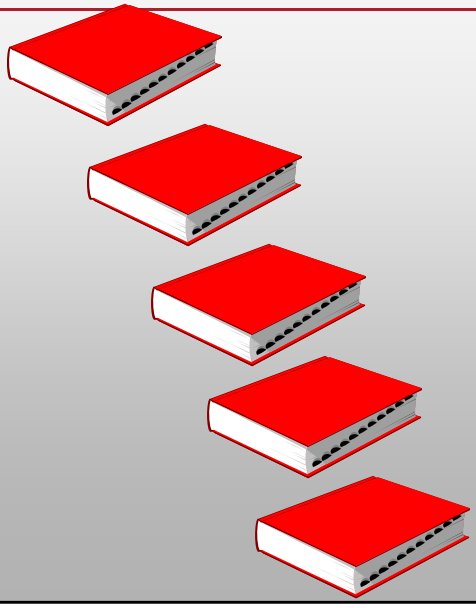
Marketing autorisation dossier



◆ **Efficacy part**

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Efficacy part

- **Pharmacological part**
  - **Pharmacodynamics**
    - Study of effects of active substance in the body
  - **Pharmacokinetics**
    - Study of effects of body in the substance
    - Study of the time course of drug absorption, distribution, metabolism and excretion (ADME)
- **Efficacy trials**

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Pharmacodynamics

1. Pharmacological class / therapeutic group

2. Mechanism of action

3. Secondary pharmacological effects (adverse reactions)

4. Efficacy concentration: *in vitro* model

- **Antiparasitic substance: Lethal concentration**
- **Antimicrobial substance: Minimal inhibitrice concentration**
- **Others substances: effect concentration**

5. Justification of fixed combination

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Pharmacokinetics

PK study in animals

- **Support studies on clinical efficacy, tolerance and safety for consumer**
- **Obtain basic PK parameters**
- **Estimate ADME of active substance**

- 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

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Pharmacokinetics

- 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

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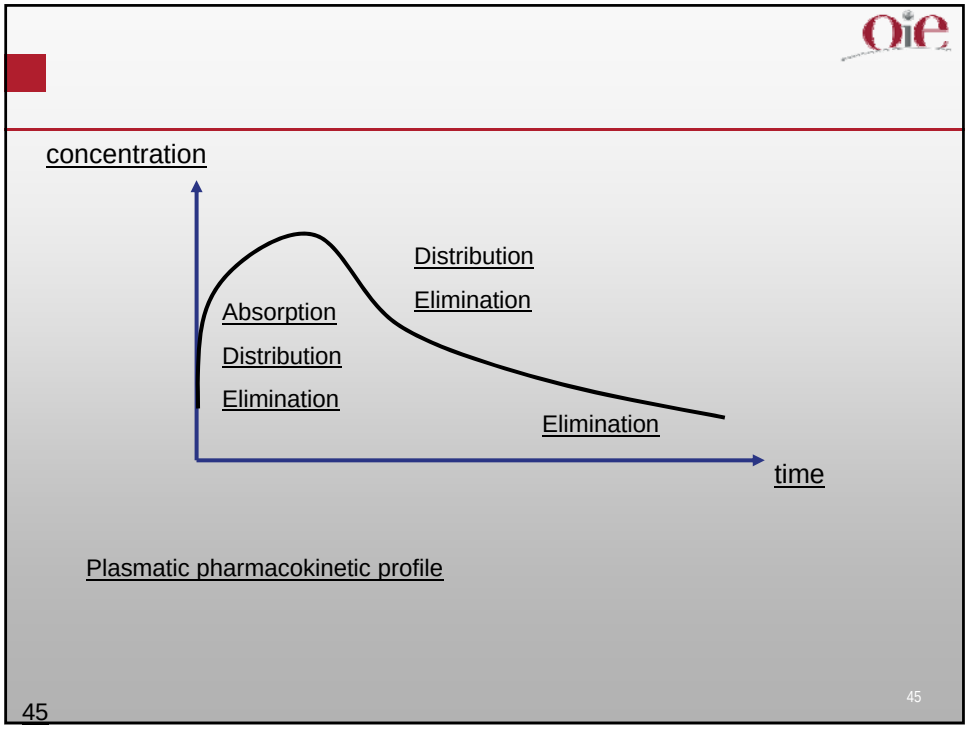

Plasmatic pharmacokinetic profile

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Pharmacokinetics

- **Bioavailability** study
- **Linearity** according to the dose
- **Gender** influence
- **Food** influence if VMP administered during the meal
- **Bio-equivalence** if generic
- **Plasma protein binding** test

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PK/PD analysis

The PD and PK data should be related to the dose/effect findings to determine adequate exposure

Establish effective dosage regimen

- **Route & site of administration**
- **Dose**
- **Dosing interval**
- **Number of administration**

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CLINICAL TRIALS

- **Definition**

The goal of clinical trials is to demonstrate the efficacy of a Veterinary Medicinal Product (VMP) after administration at the recommended dose, and specify:

- **indications and contra-indications for the target species (age, breed, sex);**
- **recommandations for use;**
- **adverse effects;**
- **safety and tolerance for normal use.**

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CLINICAL TRIALS

- General principles

Clinical trials:

- **experimental infections**
- **field conditions**

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- Immunologicals

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ANALYTICAL FILE

- A - Composition
- B - Manufacturing process
- C - Controls of starting materials
- D - In-process controls
- E - Controls of finished product
- F – Consistency of production
- G - Stability

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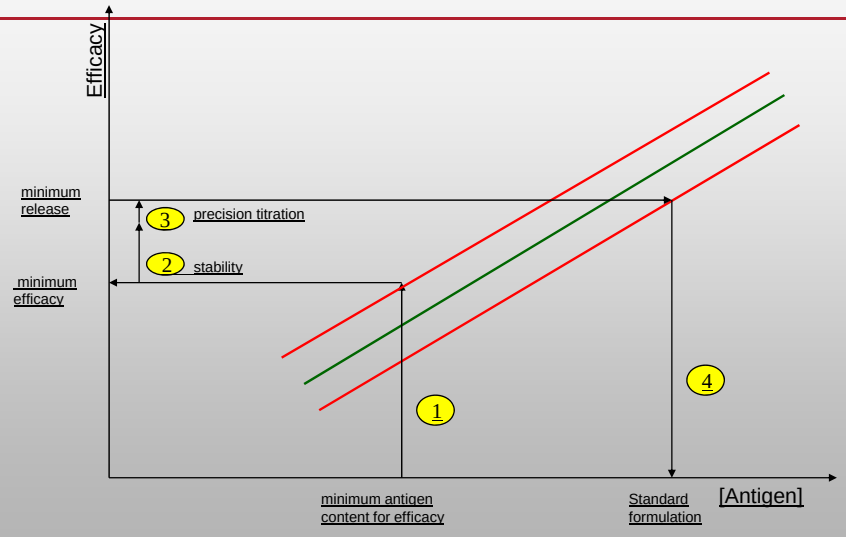
FORMULATION – PRINCIPLES



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C - CONTROL OF RAW MATERIALS

- **cells**
  - ➔ **cell lines / primary cells**
  - ➔ **master seed lot / working seed lot**
- **eggs**
  - ➔ **commercial eggs**
  - ➔ **eggs produced by SPF flocks**

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C - CONTROL OF RAW MATERIALS

- **virus, bacteria**
  - ➔ **master seed lot**
  - ➔ **working seed lot**
  - ➔ **active ingredient**

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C - CONTROL OF RAW MATERIALS

- **Extraneous agents (+++)**
  - ➔ **List**
  - ➔ **we can only find what we are searching for**
  - ➔ **Specific or non-specific detections**
  - ➔ **Sensitivity of the detection method**

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C - CONTROL OF RAW MATERIALS

- **Others**
  - ➔ **inactivation : heat, irradiation, …**
  - ➔ **Validation of the method used**
  - ➔ **Reach the core !**
  - ➔ **Spiking reduction of 6 log10**

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F - CONTROL OF FINISHED PRODUCT

- General characteristics
- Identification and assay of active substance(s)
- Identification and assay of adjuvants and excipients
- Safety tests
- Sterility and purity
- Inactivation
- Residual humidity
- Consistency of production

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Type of vaccine / type of controls (finished product)

- Live → Eur. Ph. monograph
  → titration
- Inactivated → Eur. Ph. monograph
  → Efficacy trial (model)
  → analytical/quality

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G - STABILITY

- Claimed duration + 3 months
- Control of finished product
- Modelling

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SAFETY FILE

- Laboratory tests
- Field studies
- Ecotoxicity

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SAFETY FILE

- **Laboratory tests (batch with maximum titre)**
  - **Administration of one dose, of an overdose**
  - **Repeated administration of a dose**
  - **Reproductive performance**
  - **Immunological functions**
  - **Special requirements for live vaccines**
    - spreading, dissemination, reversion to virulence, recombination/rearrangement, biological properties (ex : tropisms)
  - **Interactions**

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SAFETY FILE

- **Ecotoxicity : GMO case**
  - **Informations on interactions between GMO and environment**
    - Characteristics affecting survival, multiplication, dissemination
    - Interactions with environment
  - **Plans : monitoring, control, waste material and emergency intervention**

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EFFICACY FILE

- **Laboratory trials**
- **Field trials**

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EFFICACY FILE - LABORATORY

- **Batch with minimum titre**
- **Challenge**
  - **Choice of the challenge strain**
  - **Animal**
    - Passive / Active Immunisation
    - Physiological status
    - Age at injection

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EFFICACY FILE - LABORATORY

- **Challenge**
  - **Protocol**
    - Model / natural conditions
  - **Moment of challenge**
    - “immediate” efficacy
    - Onset of immunity
    - Duration of immunity

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EFFICACY FILE - FIELD

- **NATURAL CHALLENGE (if possible)**
- **BATCH WITH STANDARD TITRE(S)**

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SAFETY AND EFFICACY

Comparison laboratory / field trials

Laboratory	Field
Defined animals (EOPS) / controls	Real target population
Controled immunological status (maternal antibodies)	Immunological status as is
Limited number of animals	Higher number of animals
Precise follow-up / clinical criteria	Zootechnical criteria
Controled environment	Healthy / contaminated environment

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Thank you for your attention

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