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Animal Health

Risk Assessment Veterinary Medicinal Products

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Veterinary Medicinal Product
VMP

Marketing Authorisation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Dossier for application for Marketing Authorisation as VMP

- Part 1: Summary of the Dossier
- Part 2: Pharmaceutical Information
- **Part 3: Safety + Residues**
- Part 4: Efficacy

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Safety

- Animal Safety
- Human Safety
- Environmental Safety

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Animal Safety

- Toxicity — active ingredient: rat, rabbit, etc
- Tolerance — final formulation: target species

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Human Safety

- User Safety
- Consumer Safety

User Safety

Definition of User:

Any person that may come in contact with the VMP:

- before
- during
- after

its application

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Human Safety

- User Safety

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Human Safety

- User Safety

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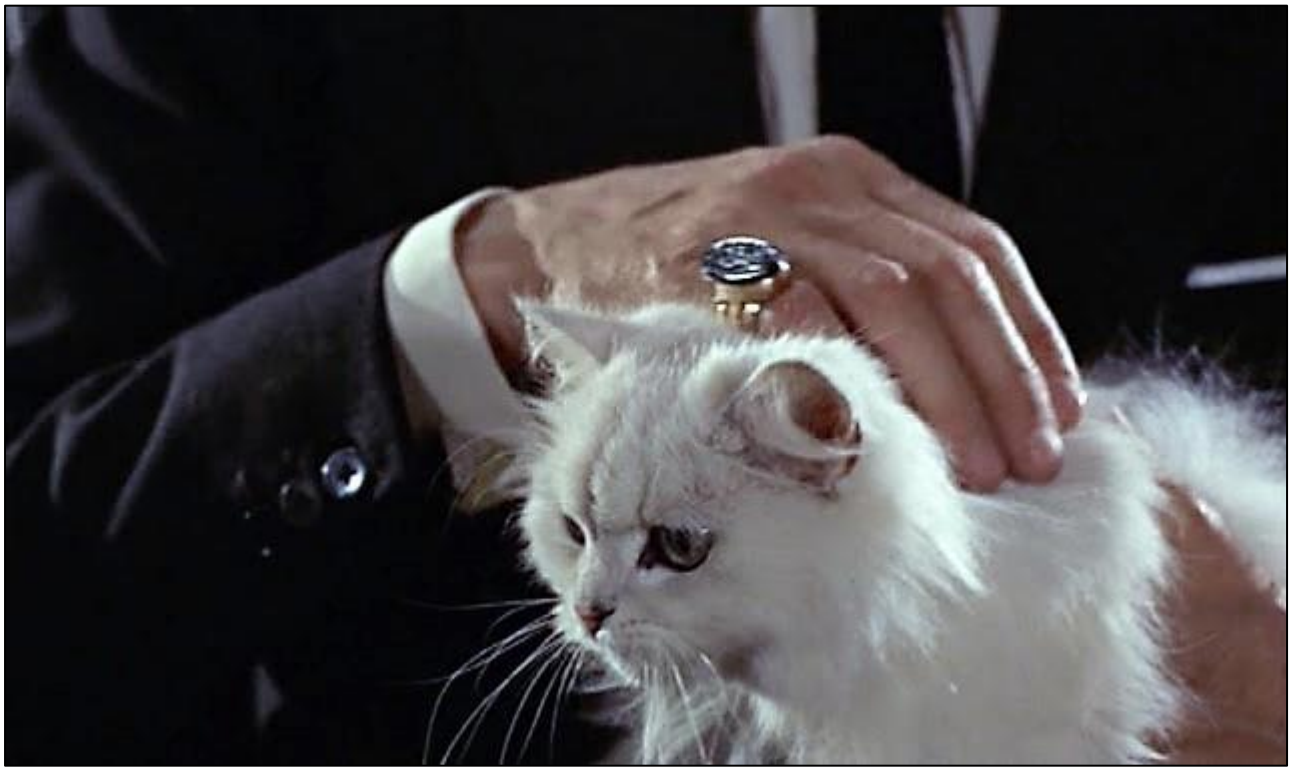
Human Safety

- User Safety



User Safety

User Risk Assessment:

- Hazard identification and characterisation
- Exposure
- Risk

User Safety

User Risk Assessment:

- Hazard identification and characterisation
  - Toxicity active(s)

NO(A)EL

User Safety

User Risk Assessment:

- Hazard identification and characterisation
- Exposure
- Risk

User Safety

User Risk Assessment:

- Exposure
  - Presentations, use, physico-chemical properties
  - Tasks and situations that lead to exposure
  - Exposure scenarios

User Safety

User Risk Assessment:

- Exposure: Tasks and situations
  - **Before** application:
    - Storage
    - Opening Package, taking out tablet
    - Mixing
    - Diluting
    - Filling syringe

User Safety

User Risk Assessment:

- Exposure: Tasks and situations
  - **During** application:
    - Administration
    - Holding/restraining animal for treatment

User Safety

User Risk Assessment:

- Exposure: Tasks and situations
  - **After** application:
    - Cleaning equipment
    - Disposal packaging
    - Disposal surplus product
    - Handling treated animals
    - Stroking the coat of treated animals

User Safety

User Risk Assessment:

- Exposure
  - Presentations, use, physico-chemical properties
  - Tasks and situations that lead to exposure
  - Exposure scenarios

User Safety

User Risk Assessment:

- Hazard identification and characterisation
- Exposure
- Risk

User Safety

User Risk Assessment:

- Risk
  - Risk characterisation
  - Risk management
  - Risk communication

User Safety

User Risk Assessment: **Topical administration**

Product:

Spot-on solution, pipette; Cat

Contact with the product

Exposure, worst-case:

Pre-application: accidental oral, child (12.5 kg)

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User Safety

User Risk Assessment: **Topical administration**

Product:

Spot-on solution, pipette; Cat

Contact with the product

<u>Exposure, worst-case:</u>

Direct oral exposure: 10 % of contents

In-direct oral exposure: 10% x 10% = 1% of contents

$$Exposure = \frac{Contents\ x\ Fraction}{Body\ weight}$$

User Safety

User Risk Assessment: **Topical administration**

Product:

Spot-on solution, pipette; Cat

Contact with the treated animal

Acute Dermal Exposure

User Safety

User Risk Assessment: Acute Dermal Exposure

DE = Dermal Exposure (mg/kg bw/day)

TR = Transferable Residue: concentration of the active per surface area of the cat that may transfer to the child (mg/cm^2)

$SA_{contact}$ = surface area child in contact with the animal (= 1790 cm^2)

$$DE = \frac{TR \times SA_{CONTACT}}{BW}$$

User Safety

User Risk Assessment: Acute Dermal Exposure

TR =Transferable Residue (mg/cm^2)

AR = Application Rate: amount of active applied to the animal (mg)

F_{AR} = Fraction of the Application Rate (= 15%)

SA_{ANIMAL} = Surface Area of the animal (cat 2500 cm^2)

$$TR = \frac{AR \times F_{AR}}{SA_{ANIMAL}}$$

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Human Safety

- Consumer Safety

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Consumer Safety

Residues → Withdrawal Period

Consumer Safety

Withdrawal period:

Period after last administration during which consumption of meat, eggs and milk is not safe, because of residues of the veterinary medicinal product

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Basis for the establishment of the withdrawal period:

MRL

Maximum Residue Limit

Consumer Safety

MRL is established by EMA on the basis of MRL-dossier submitted by veterinary pharmaceutical company.

New active? → MRL dossier

Consumer Safety

MRL is established by EMA on the basis of MRL-dossier submitted by veterinary pharmaceutical company.

New active? → MRL dossier

No MRL for the active? → No Marketing Authorisation

Consumer Safety

MRL should be established:

- For each edible tissue
- For each target species

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Edible Tissues

Mammals	**Poultry**	**Fish**	**Bees**
Muscle	Muscle	Muscle+Skin	Honey
Liver	Liver		
Kidney	Kidney		
Fat Skin+Fat (pig)	Skin+Fat		
Milk	Eggs		

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Basis to determine MRL:

- Acceptable Daily Intake (ADI)
- Body Weight Consumer
- Consumption Figures
- Marker Residues
- Distribution in Edible Tissues

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MRL Dossier

Toxicity studies $\rightarrow$ NO(A)EL $\rightarrow$ ADI

Acceptable daily intake (ADI): the estimate of the residue (μg/kg or mg/kg of bodyweight), that can be ingested daily over a lifetime without any appreciable health risk.

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MRL Dossier: Toxicity studies

- Repeated dose 90-day oral studies: rat, dog
- Repeated dose (chronic) toxicity studies: rat
- Two-generation reproduction study: rat
- Development toxicity: rat, rabbit
- Battery of mutagenicity

Additional studies:

- Carcinogenicity studies
- Other tests: Immunotoxicity, neurotoxicity, etc

In compliance with GLP (Good Laboratory Practice)

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MRL Dossier: Toxicity studies $\rightarrow$ NO(A)EL

NO(A)EL	Animal toxicity data
ADI	Human beings

Determination ADI:

$$ADI = \frac{NO(A)EL}{UF}$$

UF = Uncertainty (Safety) Factor

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MRL Dossier, Residue File

?

ADI → MRL

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MRL Dossier, Residue File

Maximum acceptable residue daily intake to be ingested by the consumer:

Body weight **60** kg

Maximum intake: $ADI \times 60$

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MRL Dossier, Residue File

?

ADI x 60 → MRL

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MRL Dossier, Residue File

ADI x 60 → MRL

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MRL Dossier, Residue File

ADI x 60 → MRL

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Consumer Safety

MRL Dossier

ADI x RL

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Consumer Safety

MRL

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MRL Dossier

Food basket Daily Consumption

Mammals	(kg)	Poultry	(kg)	Fish	(kg)
Muscle	0.300	Muscle	0.300	Muscle+skin	0.300
(Skin+) Fat	0.050	Skin+ Fat	0.090		
Liver	0.100	Liver	0.100		
Kidney	0.050	Kidney	0.010		

PLUS

Milk	1.500	Eggs	0.100	Honey	0.020

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MRL Dossier

Basis to determine MRL:

- Acceptable Daily Intake (ADI)
- Body Weight Consumer
- Consumption Figures
- Distribution in Edible Tissues

Consumer Safety

MRL Dossier

<u>Distribution in edible tissues</u>

MRLs should be based on the tissue residues distribution pattern of the active substance

Consumer Safety

MRL Dossier

Distribution in edible tissues

MRLs should be based on the tissue residues distribution pattern of the active substance

Determination of distribution:

Tissue residue study

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Tissue Residue Study

For example:

Target Species: Cattle

ADI: 1.50 μg/kg

Body Weight 60 kg → Max Daily Intake: **90** μg

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Tissue Residue Study

<u>Design</u>

24 animals: Cattle

6 groups, 4 animals each

Administration active

Slaughtering: 3, 6, 9, 12, 15, 18 days post dosing

Analyses: concentration in liver, kidney, fat, muscle

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Tissue Residue Study

	Residues (μg/kg)				
Days post dosing	Liver	Kidney	Fat	Muscle	
3	799	1022	213	75.1	
6	567	665	150	57.3	
9	335	307	86.8	39.6	
12	221	197	59.3	29.5	
15	106	86.8	31.9	19.4	
18	76.9	65.0	21.7	13.2	

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Tissue Residue Study

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18	76.9	65.0	21.7	13.2	
Food basket	0.100	0.050	0.050	0.300	kg

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Tissue Residue Study

	Residues (µg/kg)				
Days post dosing	Liver	Kidney	Fat	Muscle	Total ingested (µg)
3	799	1022	213	75.1	164
6	567	665	150	57.3	115
9	335	307	86.8	39.6	65.1
12	221	197	59.3	29.5	43.7
15	106	86.8	31.9	19.4	22.4
18	76.9	65.0	21.7	13.2	16.0
Food basket	0.100	0.050	0.050	0.300	kg

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Tissue Residue Study

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Food basket	0.100	0.050	0.050	0.300	kg

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Tissue Residue Study

	Residues (μg/kg)				
Days post dosing	Liver	Kidney	Fat	Muscle	Total ingested (μg)
9	335	307	86.8	39.6	65.1
Distribution	*8*	*8*	*2*	*1*	*Max Daily Intake*
MRL possible	240	240	60	30	48.0
MRL possible	320	320	80	40	64.0

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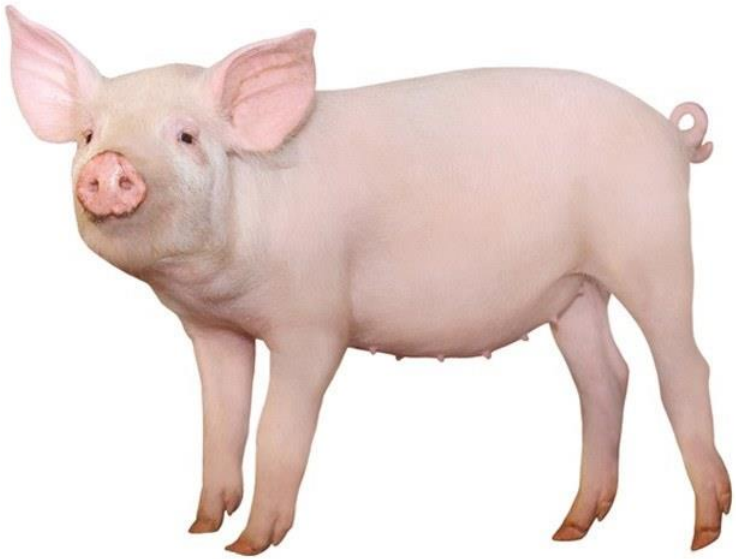
MRL → Withdrawal period

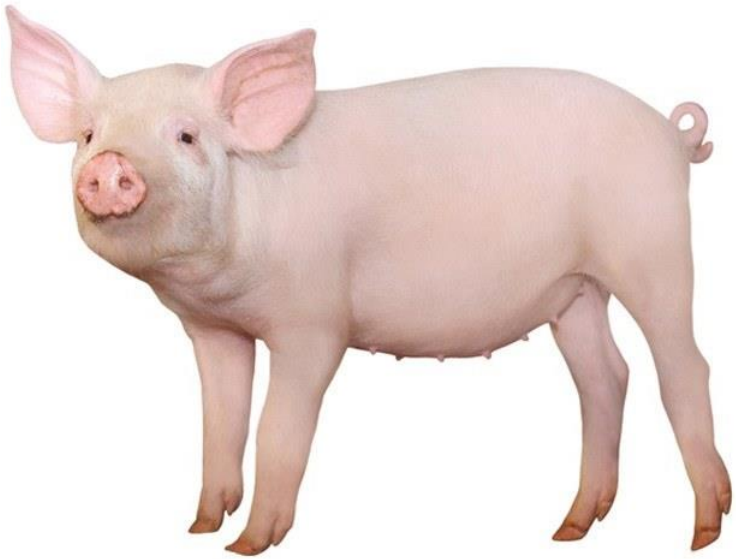


Consumer Safety

Withdrawal period:

Withdrawal period depends on the individual formulation

Marketing Authorisation Dossier!



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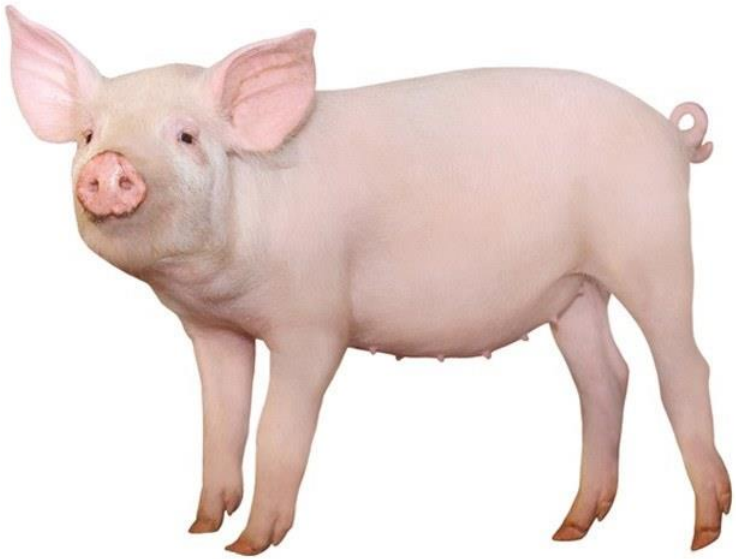
Withdrawal period:

Tissue Residue Study



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Withdrawal period:

Tissue Residue Study

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Tissue Residue Study

- Final Formulation!!!
- Target Species
- Dosing according to Marketing Authorisation
- Good Laboratory Practice

Consumer Safety

Tissue Residue Study

Design, for example:

- Cattle
- 4 groups, 6 animals each
- Slaughtering groups at 7, 14, 21, 28 days post dosing
- Analyses liver, kidney, muscle, fat

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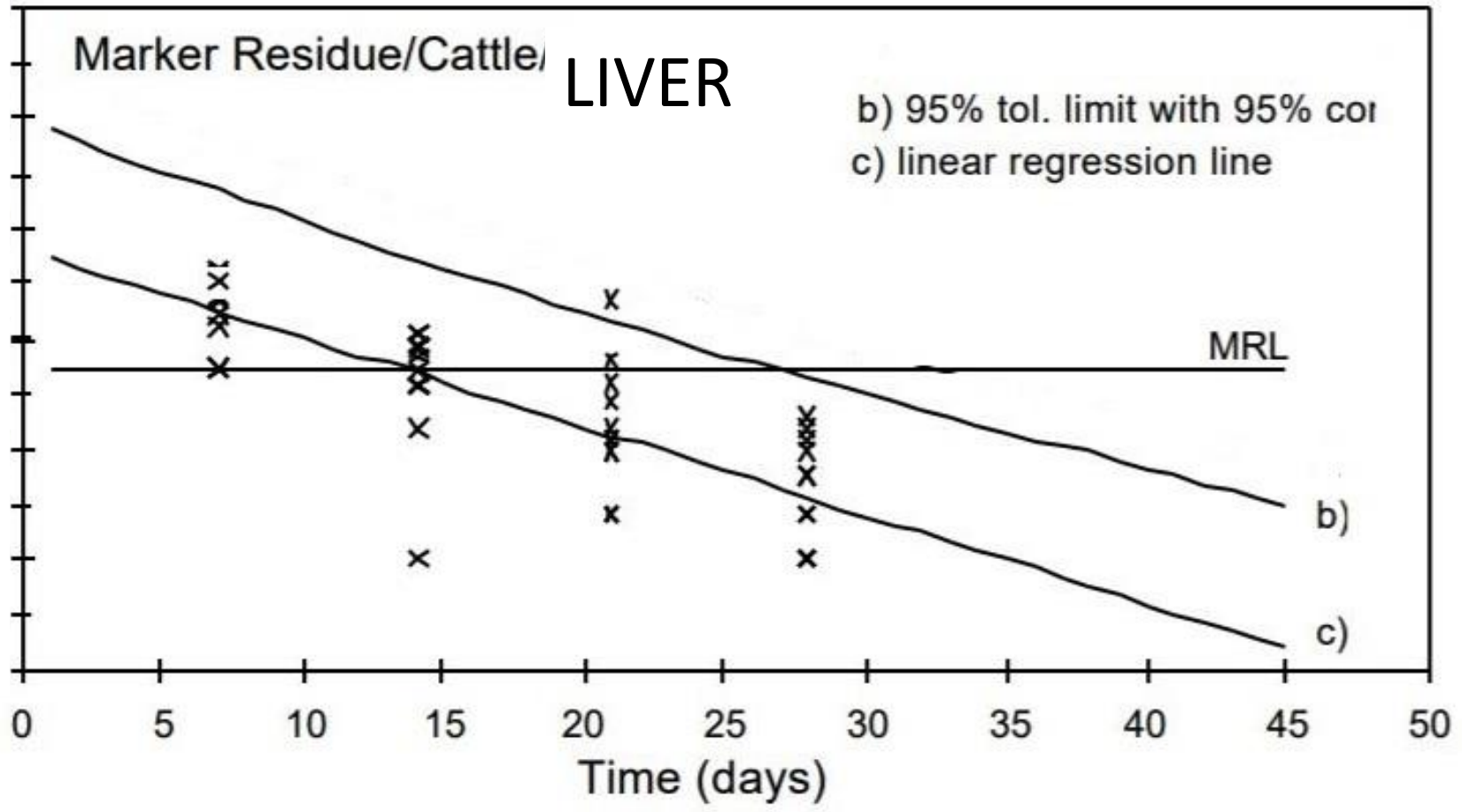

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Withdrawal Periods

Liver	28 days
Kidney	10 days
Muscle	14 days
Fat	10 days

Overall Withdrawal Period: 28 days

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Product on the market:

Pharmacovigilance

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