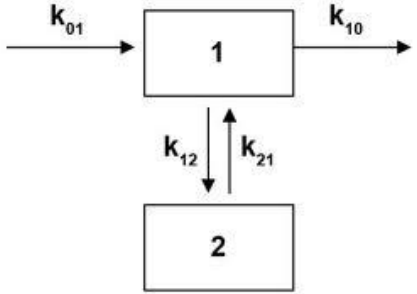
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Focus group meeting the pilot project on dose optimisation of established veterinary antibiotics in the context of SPC harmonisation

Dose dependent Withdrawal Periods



Focus group meeting, 12 October 2018, London

Presented by Peter Hekman
CVMP Member

WITHDRAWAL PERIODS:

- In general, the methods of calculating withdrawal periods (WPs) can be defined as a mutually agreed way, to use and treat the experimental data of residue depletion studies in order to calculate a WP.

- Since 1997/1998 the methods have been harmonized (CVMP guidelines) to:
  - ensure Consumer safety
  - guarantee a level playing field for MAH's regarding the estimation of WPs.

- It is acknowledged that these methods can be considered a pragmatic compromise between science and feasibility.

CURRENT SITUATION:

- Dossiers of the VMP's involved often contain old residue studies. non-GLP, using old analytical methods, but often representing field conditions.
- Even when the same residue depletion data are available, the same products may have different WP's in the different Member States.
- Only a few residue depletion studies covering a large amount of VMP's (e.g. 11 residue studies covering 287 authorizations).
- Studies often failed to meet the statistical demands, leading to the use of the so-called alternative method, applying safety margins.
- Recent studies comply with the statistical criteria, but are designed to minimize inter-animal variance, and are less representative of field conditions.

- The method proposed for the extrapolation of WP's is similar to the algorithm used by FARAD (Food Animal Residue Avoidance Databank) since 2002

$$WP_{new} = WP_{old} + \{\log_2(F_{rel} \times D_{new}/D_{old}) \times T_{1/2}(\text{final phase})\}^{\text{rounded up}}$$

F_{rel} = Relative bioavailability new dose/old dose;

$T_{1/2}$ = Half-life (days; rounded up) in WP determining tissue(s)

WP = Withdrawal period (days)

D = Dose (mg/kg);

- It is assumed that the dosing frequency and duration will not change. If the dosing interval/duration would change, FARAD subroutines can be used.

Conditions:

- Linear kinetics (for all ADME-processes) apply

- At MRL-level….tissue distribution is complete

- Withdrawal Period > 0

EXTRAPOLATION METHOD:

1. Establish the general pharmacokinetic particulars of VMP/active substance/residues involved, such as:
    a. Do linear kinetics apply for the intended dose range (yes/no)
    b. Relative bioavailability new dose (default Frel=1)
    c. General ADME particulars (e.g. active transport)
2. Establish the terminal half-life in tissues/milk/eggs
3. If conditions (linear kinetics and complete distribution) are fulfilled, calculate the WP (extrapolated). Apply algorithm to each VMP separately.
4. If conditions are not fulfilled, perform further kinetic modelling, and apply adjusted and validated model to each VMP separately, calculating a new WP.

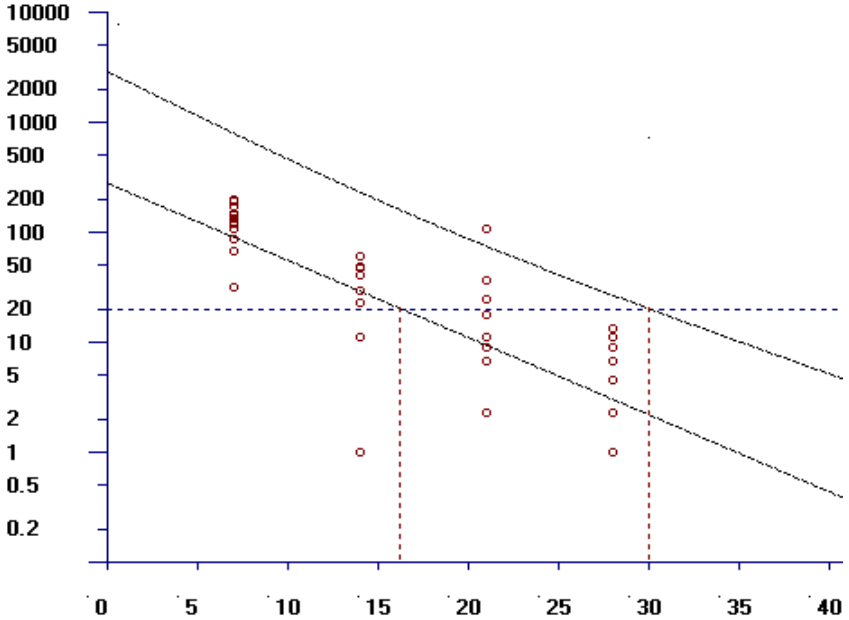
DATA SOURCES:

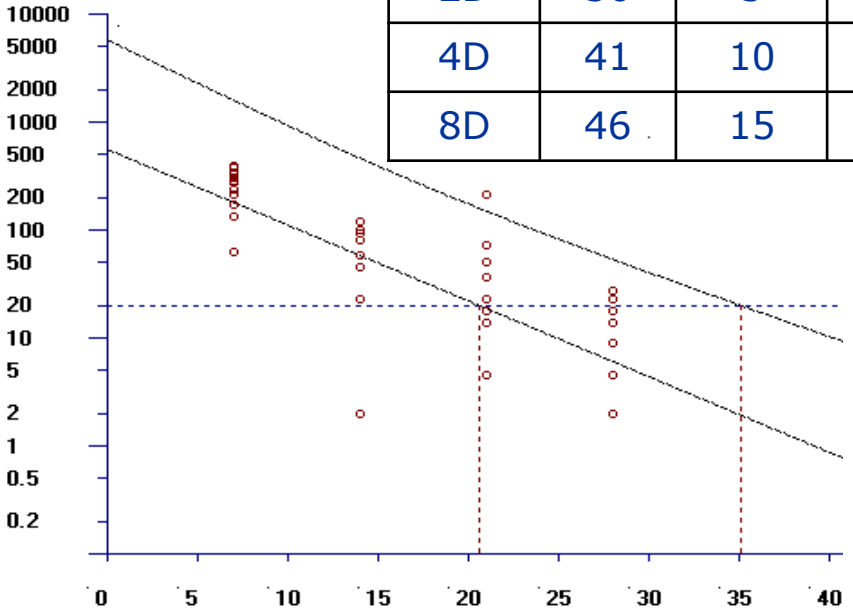
- Dossier data
- FARAD database
- Public Assessment Reports (if available)
- International Journals (peer reviewed)
- Publications by public committees (e.g. EMA/JECFA/EFSA)

Example Tissues/Organs:

Dose	WP stat	Delta stat	Delta calc.
D	31	-	-
2D	36	5	5
4D	41	10	10
8D	46	15	15

Residue Data: Liver Tissue (from guideline)

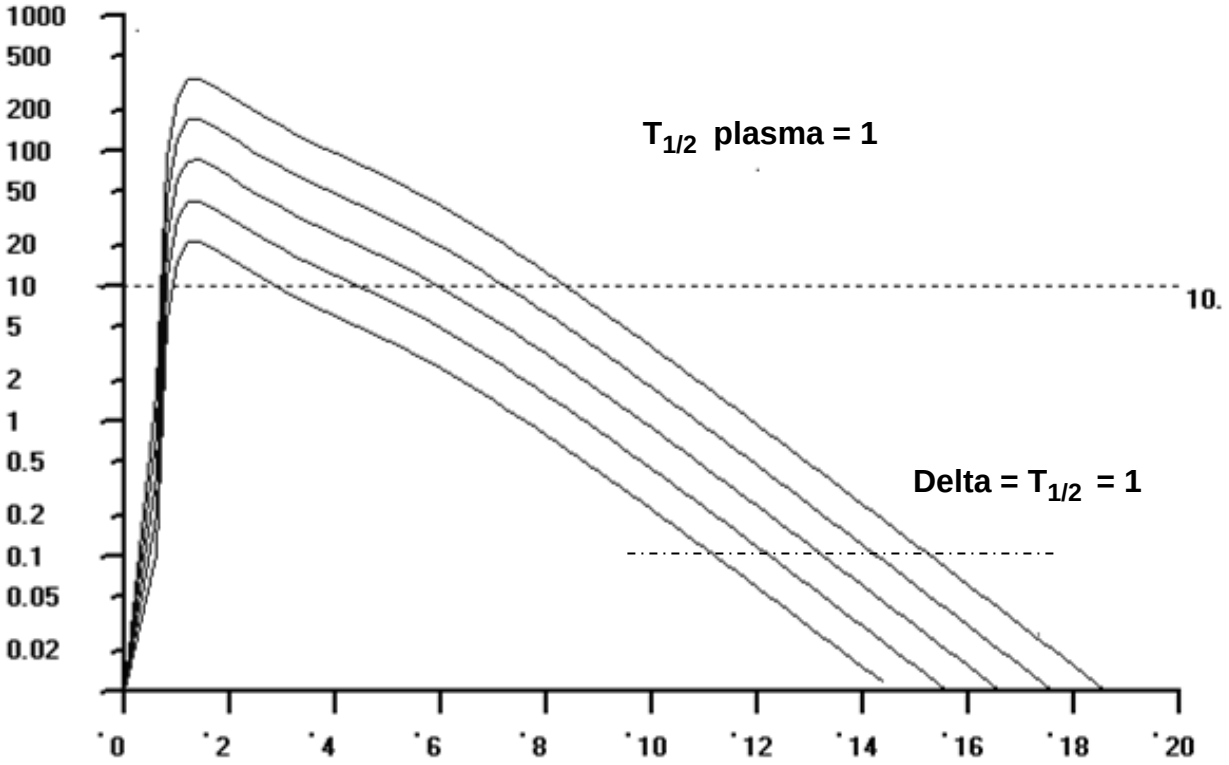




Example Eggs:

Linear 1 comp model P.O.

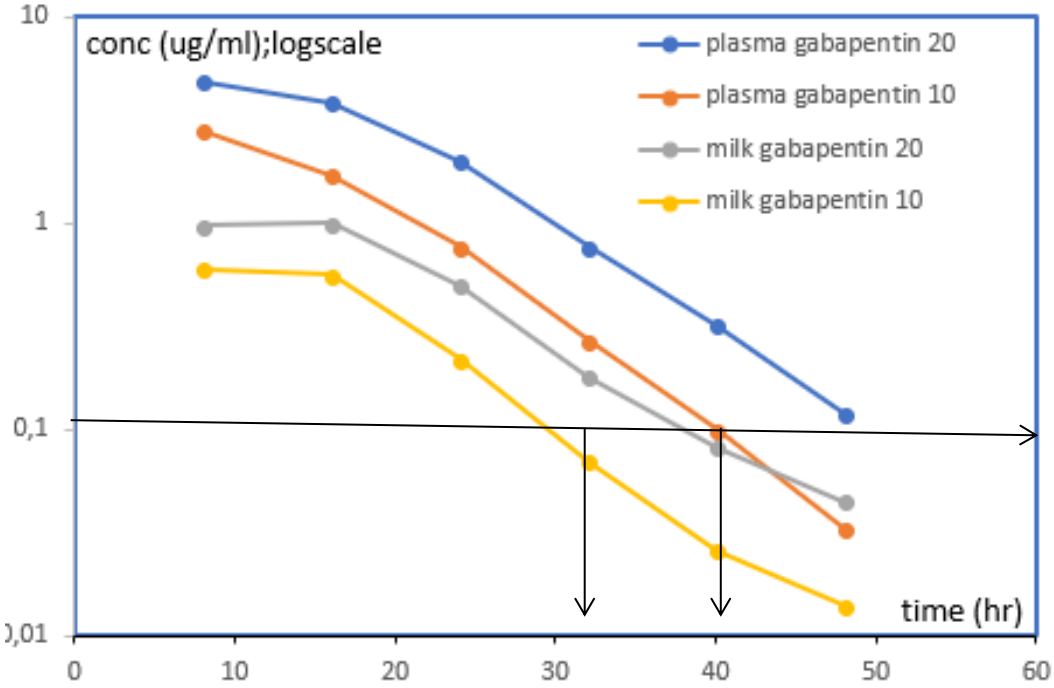
Dose	WP	delta
D	2.8	-
2D	4.4	1.6
4D	5.9	1.5
8D	7.2	1.3
16D	8.4	1.2



Example Milk:

The WP of the 20 mg/kg dose was calculated based on 8 hr milking interval and a mean $T_{1/2}$ = 6.2 h (lin. Regression)

Dose (mg/kg)	WP milk (h)	WP milk (h)
10	32	-
20	40	40



Thank you for your attention

Further information

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