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

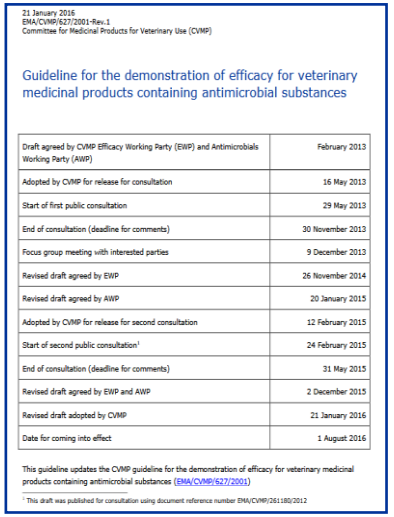
PK/PD approach for dose optimisation

Focus group meeting, 12 October 2018, London

Presented by Damien Bouchard[1] and Pascal Sanders[2]
Anses – [1]French Agency for Veterinary Medicinal Products and [2]Laboratory of Fougères

Applicability of PK/PD modelling approaches to address doses (1)

The revised guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1) specifies the data required to demonstrate the therapeutic efficacy of a veterinary medicinal product (VMP) containing an antibacterial agent for (a) given indication(s) using an appropriate therapeutic regimen.



21 January 2016
EMA/CVMP/627/2001-Rev.1
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances

Draft agreed by CVMP Efficacy Working Party (EWP) and Antimicrobials Working Party (AWP)	February 2013
Adopted by CVMP for release for consultation	16 May 2013
Start of first public consultation	29 May 2013
End of consultation (deadline for comments)	30 November 2013
Focus group meeting with interested parties	9 December 2013
Revised draft agreed by EWP	26 November 2014
Revised draft agreed by AWP	20 January 2015
Adopted by CVMP for release for second consultation	12 February 2015
Start of second public consultation[1]	24 February 2015
End of consultation (deadline for comments)	31 May 2015
Revised draft agreed by EWP and AWP	2 December 2015
Revised draft adopted by CVMP	21 January 2016
Date for coming into effect	1 August 2016

This guideline updates the CVMP guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001)

[1] This draft was published for consultation using document reference number EMA/CVMP/261180/2012

Based on:

- MIC data,
- target animal PK data

= an analysis for the PK/PD relationship may be used to support dose regimen selection and interpretation criteria for resistance.

Presented by Damien Bouchard(1) and Pascal Sanders(2)

Applicability of PK/PD modelling approaches to address doses (2)

- the PK/PD approach **has been recognised as an important tool** for the development of new antibiotics as a way **to integrate different data** about antibacterial efficacy, pharmacology and bacteriology during product development (Drusano, 2016).
- Based on the analysis of **clinical trials, experimental in vitro and in vivo studies**, and mathematical models, **a relationship between clinical and bacteriological targets and PK/PD was established** (Ambrose et al., 2007).
- The relationship between a pharmacokinetic parameter and a pharmacodynamic parameter to predict clinical efficacy is labelled as a **PK/PD index** (PDI)
- In human health, the PK/PD approach is also used in the process of definition of a clinical breakpoint by **EUCAST** (Mouton et al., 2012).
- The methodology is also proposed by **VetCAST** to define clinical breakpoints (CBPs) for antimicrobial drugs (AMDs) used in veterinary medicine in Europe (Toutain et al., 2017)

Data requirements in order to use the PK/PD analysis approach for dose optimisation

- PK data
  - PK raw data from studies for individual product
  - Mean values for each PK parameters (CL, F, f …)
- PD data
  - MIC distribution for each target bacteria

Minimal information required

Furthermore, the following data would be desirable:

- Time-kill curves
- PK/PD modelling
- Literature search
- *In vivo* experiment - correlation between prediction and clinical outcome

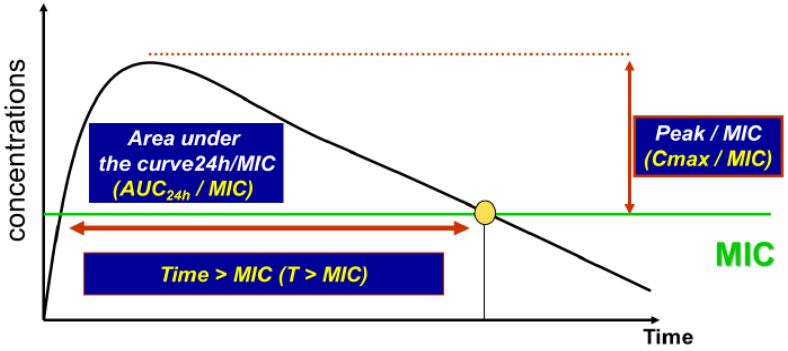
Presented by Damien Bouchard[1] and Pascal Sanders[2]

How to revise a dose using the PK/PD approach

Step 1
Selection of PK/PD index predictive of clinical efficacy or prevention of resistance
(concentration versus time-dependent ATM)

Step 2
Determination of the critical value of the PK/PD index

Step 3
Computation for a given animal species and for all possible MIC, of the percentage of animals able to achieve the critical value of the selected PK/PD index (Probability of Target Attainment – PTA)



from Toutain et al., 2017: En Route towards European Clinical Breakpoints for Veterinary Antimicrobial Susceptibility Testing: A Position Paper Explaining the VetCAST Approach.

from Anses Expert report, 2017: Methodology for revising the dosages of older antibiotics. (WG chair: A. Bousquet-Melou)

Presented by Damien Bouchard(1) and Pascal Sanders(2)

How to revise a dose using the PK/PD approach

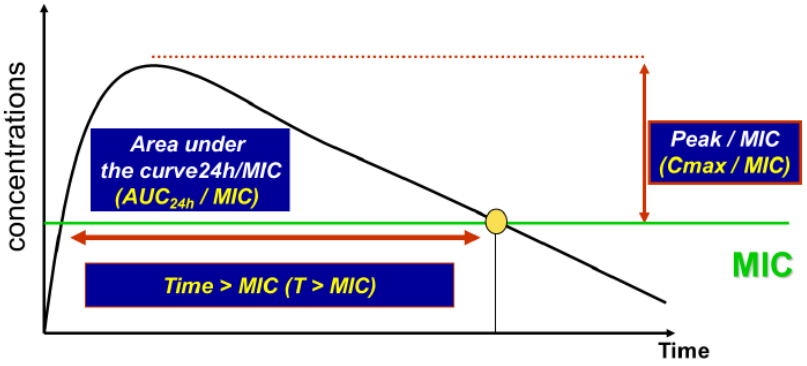
Methodology based on PK/PD using the relation between PK and dose of the antimicrobials provided by the following equation:

Equation n°1

$$Dose = \frac{Clearance}{Bioavailability} \times C_{Target}$$

How to revise a dose using the PK/PD approach

When the selected PK/PD is AUC_{24h}/MIC as an example



The following equation provide the relation between target concentration and PK/PD value to be reached:

Equation n°2

$$C_{Target} = \frac{\left(\frac{AUC}{MIC}\right)_{Critical\ value}}{24} \times \frac{MIC}{f}$$

How to revise a dose using the PK/PD approach

Equation 1

$$Dose = \frac{Clearance}{Bioavailability} \times C_{Target}$$

Equation 2

$$C_{Target} = \frac{\left(\frac{AUC}{MIC}\right)_{Critical\ value}}{24} \times \frac{MIC}{f}$$

When combining equation 2 to equation 1:

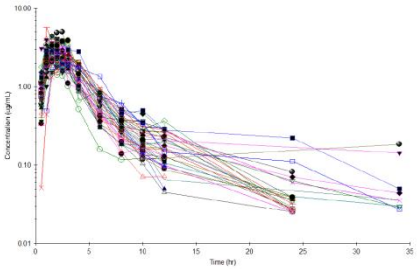
$$Daily\ Dose = \frac{Clearance}{Bioavailability} \times \frac{MIC}{fu} \times \left(\frac{AUC}{MIC}\right)_{Critical\ value}$$

$$Daily\ Dose = \frac{Clearance}{Bioavailability} \times \frac{MIC}{fu} \times \left(\frac{AUC}{MIC}\right)_{Critical\ value}$$

ATB dose per time unit

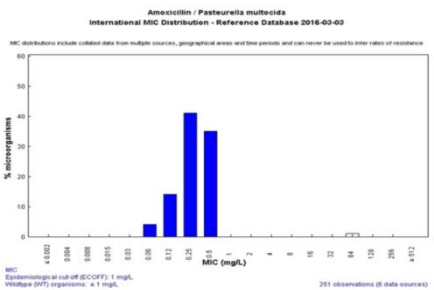
PK parameter

controlling the blood levels of the antibiotic



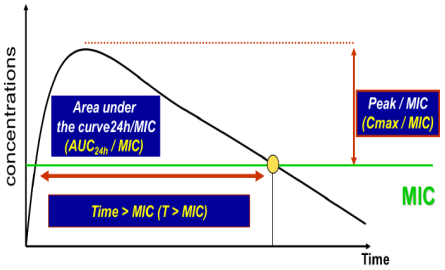
PD parameter

susceptibility of the target population



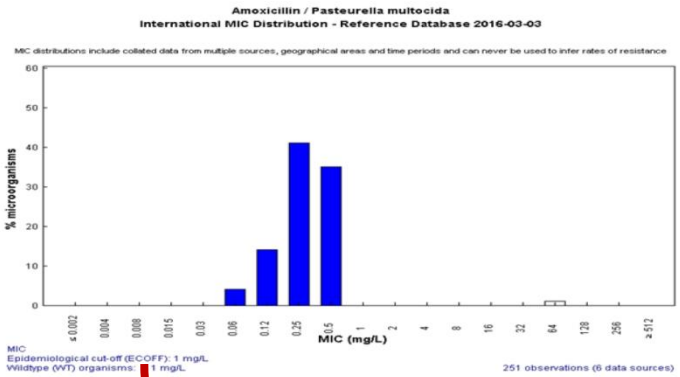
PK/PD index

dependant of the ATB class



PK/PD and Monte Carlo Simulation (MCS)
Probability of Target Attainment

Distribution of PD parameters



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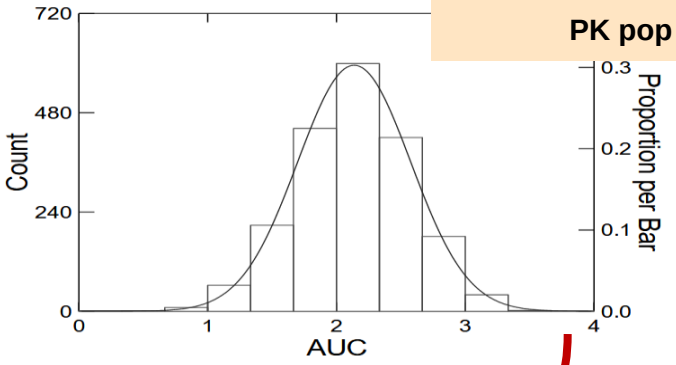
Distribution of PK parameters

Different AUC simulated PK pop



MCS: random selection of PK and PD parameters to obtain a distribution of PK/PD index (e.g. AUC/MIC)

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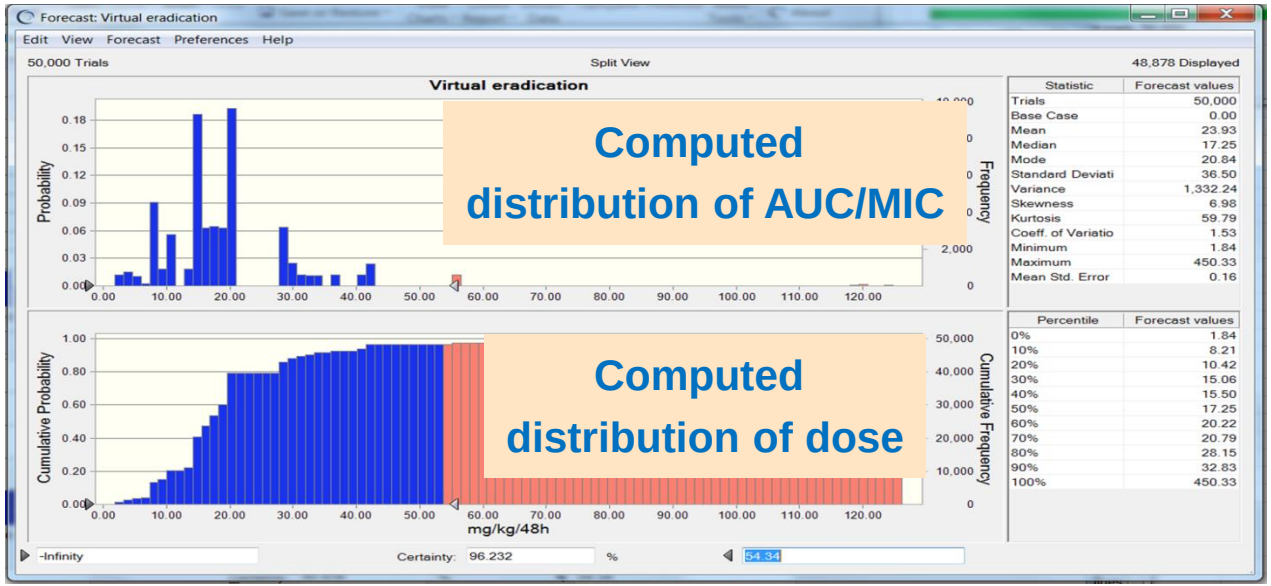
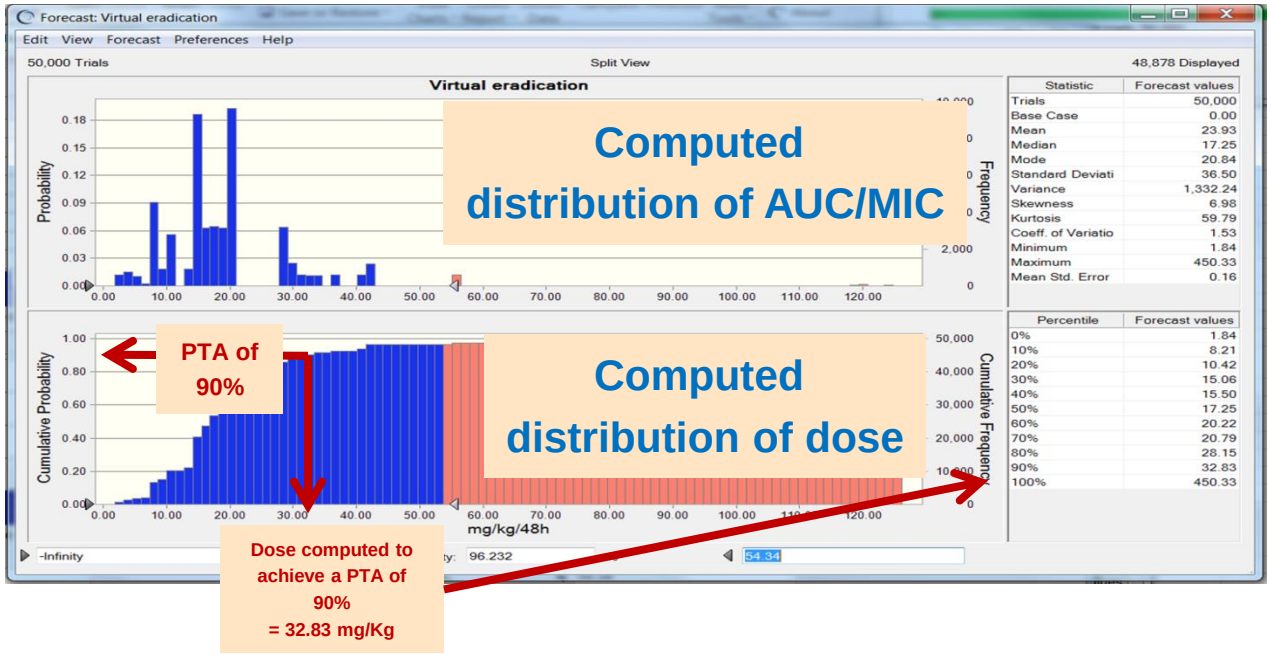
PK/PD and Monte Carlo Simulation (MCS)
Probability of Target Attainment



Dose determination to reach a PTA of 90% for a defined AUC/MIC which guarantee the clinical target (e.g. bacteriostatic or bactericidal)

PK/PD and Monte Carlo Simulation (MCS)

Probability of Target Attainment



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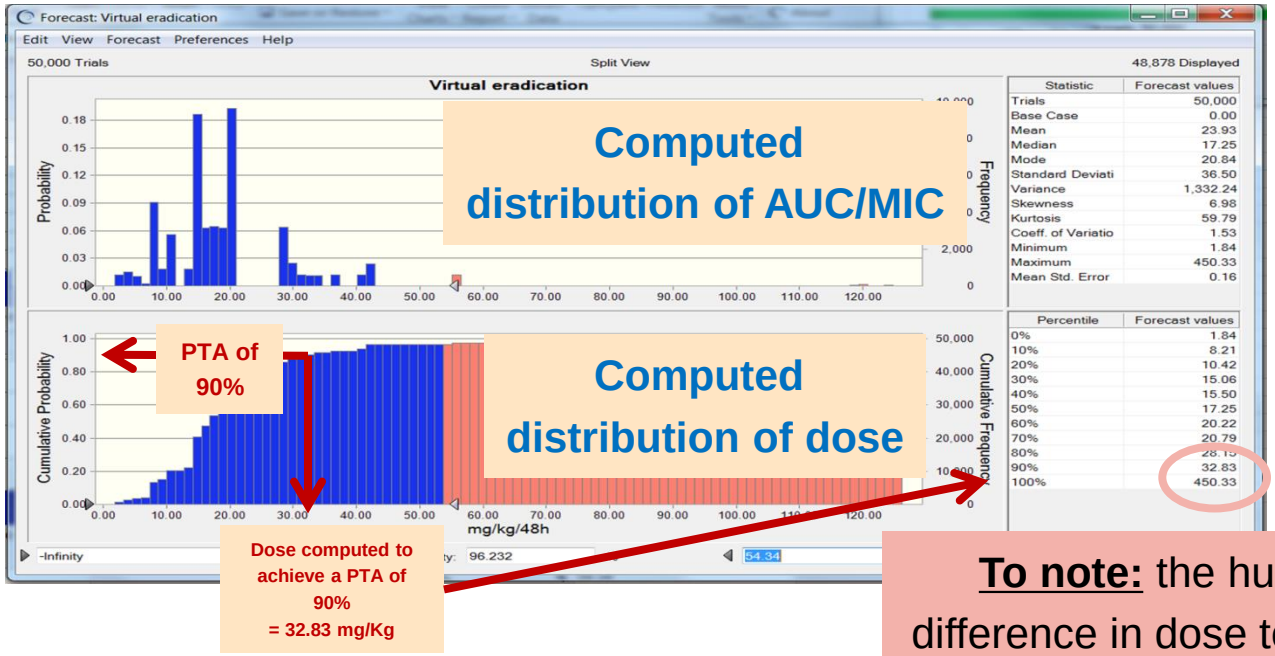

Dose determination to reach a PTA of 90% for a defined AUC/MIC which guarantee the clinical target (e.g. cteriostatic or bactericidal)

To note: the hudge difference in dose to reach 100% of the animals

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PK/PD and Monte Carlo Simulation

Probability of Target Atteinment

Example for a time dependent ATM at one predicted

MIC of the target pathogen (µg/mL)

$T>MIC_{24h}$	0.0625	0.125	0.25	0.5	1	2	4
	100	100	100	100	100	50	50
10%	100	100	100	100	100	46.85	9.75
20%	100	100	99.9	98.25	85.35	27.65	0.05
30%	99.8	98.05	92.8	77.05	50.7	6.3	0
40%	97.3	91.15	78.3	59.05	34.05	1	0
50%	93.2	83.6	67.1	48.95	20.2	0	0
60%	89	76.1	59.6	40.2	9.05	0	0
70%	85.25	70.2	53.55	32.1	3.7	0	0
80%	80.85	64.35	47.25	24.8	0.85	0	0
90%	76.9	59.85	41.35	17.5	0.2	0	0
100%	72.35	55.35	35.5	10.85	0	0	0

Use of Monte Carlo simulation to determine pharmacodynamic cutoffs of amoxicillin to establish a breakpoint for antimicrobial susceptibility testing in pigs

Julien F. Rey, DVM; Céline M. Laffont, PhD; Siska Croubels, Pharm D; Patrick De Backer, DVM; Claudine Zemirline, DVM; Eric Bousquet, DVM; Jérôme Guyonnet; Aude A. Ferran, DVM; Alain Bousquet-Melou, DVM; Pierre-Louis Toutain, DVM

IM administration 30mg/kg

Determination of the PTA according to the MIC and the T>MIC for a defined dose

PK/PD and Monte Carlo Simulation - Probability of Target Atteinment

MIC of the target pathogen (µg/mL)

Valeur de la CMI (µg/mL)

T>MIC$_{24h}$	0.0625	0.125	0.25	0.5	1	2	4
	100	100	100	100	100	50	50
[illegible]	100	100	100	100	100	46.85	9.75
20%	100	100	99.9	98.25	85.35	27.65	0.05
30%	99.8	98.05	92.8	77.05	50.7	6.3	0
40%	97.3	91.15	78.3	59.05	34.05	1	0
50%	93.2	83.6	67.1	48.95	20.2	0	0
60%	89	76.1	59.6	40.2	9.05	0	0
70%	85.25	70.2	53.55	32.1	3.7	0	0
80%	80.85	64.35	47.25	24.8	0.85	0	0
90%	76.9	59.85	41.35	17.5	0.2	0	0
100%	72.35	55.35	35.5	10.85	0	0	0

Determination of the PTA according to the MIC and the T>MIC for a defined dose

For B-lactams, need at least to achieve a PK/PD critical value equivalent to 40% of the dosing interval

Maximal MIC to obtain a PTA of 90% with a T>MIC of 40% of the interval dosing

What are the limits of the PK/PD approach ?

- the model do not take into account the **impact on gut microbiota**;
- the model use the **MIC as PD indicator**;
- the model do not take into account the **immune system of the host**;
- the model can provide information on the rhythm of administration but **not the duration of an antimicrobial course**;
- the need to **confirm or define by clinical confirmation** the critical value of the PK/PD index for each target animal species

= For old antibiotics where scientific evidences from experimental and clinical trials supporting the setting of PDI and PDT are available, the PK/PD integration approach is as eligible to dose optimisation.

Thank you for your attention

Further information

zoltan.kunsagi@ema.europa.eu
European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
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