



Rationale for EUCAST clinical veterinary breakpoints

Agent	Doxycycline (DOX) in piglets and pigs (VetCAST) for oral administration	
Current version	Version 1.0	15 May 2026
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Foreword

EUCAST

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is organised by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID), the European Centre for Disease Prevention and Control (ECDC), and the active national antimicrobial breakpoint committees in Europe. EUCAST was established by ESCMID in 1997, was restructured in 2001-2002 and has been in operation in its current form since 2002. The current remit of EUCAST is to harmonise clinical breakpoints for existing drugs in Europe, to determine clinical breakpoints for new drugs, to set epidemiological (microbiological) breakpoints, to revise breakpoints as required, to harmonise methodology for antimicrobial susceptibility testing, to develop a website with MIC and zone diameter distributions of antimicrobial agents for a wide range of organisms and to liaise with European governmental agencies and European networks involved with antimicrobial resistance and resistance surveillance.

Information on EUCAST and EUCAST breakpoints is available on the EUCAST website at <http://www.EUCAST.org>.

EUCAST rationale documents

EUCAST rationale documents summarise the information on which the EUCAST clinical breakpoints are based.

Availability of EUCAST documents

All EUCAST documents are freely available from the EUCAST website at <http://www.EUCAST.org>.

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This rationale document should be cited as: "European Committee on Antimicrobial Susceptibility Testing. Agent name: Rationale for the clinical breakpoints, version number e.g.1.0, year e.g. 2013. <http://www.eucast.org>.

1. Introduction

Doxycycline (DOXY) is a semi-synthetic bacteriostatic tetracycline with broad spectrum activity against many aerobic and anaerobic gram-positive and gram-negative bacteria.

DOXY is extensively used in pig farming (Lekagul et al., 2019) for the metaphylaxis and treatment of porcine respiratory disease caused by *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Streptococcus suis*, *Mycoplasma hyopneumoniae*, *Mycoplasma hyorhinis* susceptible to doxycycline. It is also prescribed to treat atrophic rhinitis caused by *Pasteurella multocida* and *Bordetella bronchiseptica*.

DOXY is available for oral administrations either in drinking water or feed. The typical recommended dose in pigs for the EU is 12.5 mg doxycycline hyclate (10.87 mg of doxycycline base) per kg body weight per day for 4 consecutive days but DOXY has also marketing authorization in the EU at higher approved daily doses up to about 20 mg/kg per day for 3-8 consecutive days either in feed or in drinking water (DW).

Administration of DOXY, at an average in-feed dose of 11 mg/kg/day, was shown to be effective in prevention of pneumonia caused by *P. multocida* (Bousquet et al., 1998). No field trial data were submitted to support the use of DOXY in pigs.

References

- Lekagul, A., et al. 2019 *Vet. Anim. Sci.* 7:100058.
- Bousquet, E., et al. 1998. *Vet. Rec.* 143(10):269–72.
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2. Dosage

Standard DOXY daily dose 20 mg/kg BW

Maximum DOXY daily dose 20 mg/kg BW

Available formulations Powder for use in drinking water or feed (mainly as DOXY hyclate but some formulations as DOXY hydrochloride). The conversion factor of DOXY hyclate to DOXY base is 0.866. All doses in this rationale document are expressed in terms of DOXY base. Some formulations have a licensed dose of 10 mg/kg BW

3. MIC distributions and epidemiological cut-off (ECOFF) values

MIC distributions and ECOFFs for doxycycline and tetracycline (*Bordetella bronchiseptica*) can be found at <https://mic.eucast.org/Eucast2/SearchController/search.jsp?action=init>

4. Clinical breakpoints

Existing breakpoints:

No CBP has been published for DOXY in pigs.

For tetracycline as a class representative, the CLSI-VAST CBP proposed for *S. suis*, *P. multocida* and *A. pleuropneumoniae* is $\leq 0.5, 1, >2$ for S/I and R, respectively. This CBP was derived from PK data of oxytetracycline at 20 mg/kg IM, once. The CLSI-VAST emphasises that this breakpoint is applicable only for the injectable formulations.

5. Pharmacokinetics after IV and oral (feed and drinking solution) administration (Toutain et al. 2025)

Route of administration	IV administration (NCA) (mean, range)	IV administration (NLMEM) Typical values for 10, 50 and 100 kg BW			Feed administration (NLMEM)	Drinking solution gavage administration (NLMEM)			
		10	50	100					
Body weight (kg)	Range 11.2 - 106.6 kg	10	50	100					
Total body clearance (mL/kg h)	220 (100-394)	161	259	320					
T _{1/2} (h), mean (range)	6.08 (3.26-29.2)	5.16	7.33	11.47					
Mean Residence Time (h)	5.75 (3.28-11.45)	6.7	4.7	4.7					
Volume of distribution (V _{ss}) (L/kg)	1.2 (0.49-3.1)	1.08	1.21	1.49	NA	NA			
Oral bioavailability %: Typical value and Between Subject Variability (BSV)					50% (BSV 84.8%)	30.7% (BSV 34.4%)			
Protein binding (Portugal et al. 2023)	69%								
Expected dose-dependent variables (average plasma concentration, AUCs) are reported after scaling for a typical dosage of 10 or 20 mg/kg as DOXY base for pigs weighing 10, 50 and 100 kg BW.									
Variables	IV			Feed			Drinking water		
Body weight (kg)	10	50	100	10	50	100	10	50	100
AUC(inf) in mg.h/L (10 mg/kg)	62.1	38.6	31.3	31.1	19.3	15.6	19.1	11.9	9.6
Average total plasma concentration (mg/L) over 24 h in steady-state condition (10 mg/kg)	2.59	1.61	1.30	1.29	0.80	0.65	0.79	0.49	0.40
Average free plasma concentration (mg/L) over 24 h in steady-state condition for fu=0.31* (10 mg/kg)	0.80	0.50	0.40	0.40	0.25	0.20	0.25	0.15	0.12
Average free plasma concentration (mg/L) over 24 h in steady-state condition for fu=0.31* (20 mg/kg)	NA	NA	NA	0.80	0.50	0.40	0.49	0.31	0.25
Comments	<p>Parameters and variables generated from a meta-analysis of DOXY disposition obtained in 380 individual data sets, obtained in 11 trials, conducted in three different countries, collected following DOXY administration either IV or orally in food or in DW. Pigs' BW ranged from (8.5–101 kg BW). Data analysed using either a Non-Compartmental Analysis (NCA) or a Non-Linear Mixed Effect Model (NLMEM) (Toutain et al 2025).</p> <p>Since BW is a significant covariable for plasma clearance, results are presented for 3 levels of BW (10, 50 and 100 kg BW), with 100 kg pigs having twice as high a clearance compared to 10 kg piglets. With all other PK parameters being equal across BW, this results in a twofold difference in AUC and fAUC/MIC PK/PD cutoffs, meaning piglets receive twice the drug exposure of adult pigs at the same dosage.</p>								

Reference :

- Toutain PL, Bousquet-Melou A, Ferran AA, Roques BB, Del Castillo JRE, Lees P, Croubels S, Bousquet E, Pelligand L. Pharmacokinetic-Pharmacodynamic Cutoff Values for Doxycycline in Pigs to Support the Establishment of Clinical Breakpoints for Antimicrobial Susceptibility Testing. J Vet Pharmacol Ther. 2025 Apr 17. doi: 10.1111/jvp.13511
- Portugal FR, Lacroix MZ, Roques BB, Gayrard V, Toutain PL, Bousquet-Mélou A. Doxycycline serum protein binding in pigs reveals a relatively high free fraction. J Vet Pharmacol Ther. 2023 Mar;46(2):112-118. doi: 10.1111/jvp.13111.

6. Pharmacodynamics

	Animal data
PK/PD index: <i>f</i> AUC/MIC	24.6h for <i>Streptococcus pneumoniae</i> in a murine thigh-infection model (Christianson et al., 2001) for a bacteriostatic effect. Values as low as 13 have been suggested for bacteriostatic effect against <i>S. aureus</i> (LaPlante et al. 2008).
Clinical Data	No field trial data were submitted to support the use of DOXY in pigs
Comments	According to the corresponding human EUCAST RD, the ratio of free (<i>f</i>) AUC over MIC (<i>f</i> AUC/MIC) is the dominant PK/PD index for DOXY, but there are insufficient data to determine its size for bacteriostatic or bactericidal effects in pre-clinical models and there are no supporting clinical data (EUCAST, 2009). In the present investigation, 24 h was used as the default value for bacteriostatic effect, as suggested by others (Andes et al., 2007).
References	<ul style="list-style-type: none"> • Christianson, J., et al. 2001. Clin. Infect. Dis. 33:1169. • LaPlante et al., 2008, Antimicrob Agents Chemother.;52(6):2156-62 • EUCAST. 2009. Doxycycline: Rationale for the EUCAST Clinical Breakpoints, Version 1.0. • Andes, D., et al. 2007. Pharmacokinetics and Pharmacodynamics of Tetracyclines. In: Nightingdale CH et al, Antimicrobial Pharmacodynamics Theory and Clinical Practice, 2nd Edition. CRC Press. 267–77.

7. Monte Carlo simulations and PK/PD cutoff

Probability of target attainment (PTA%) for MIC of 0.25, 0.50, 1.0 and 2.0 mg/L for pigs of 10, 50 or 100 kg BW when DOXY is administered in feed (blue curves) or in drinking water (DW, red curves) at a daily dose of 5 and 10 mg/kg (A) or 15 and 20 mg/kg BW (B).

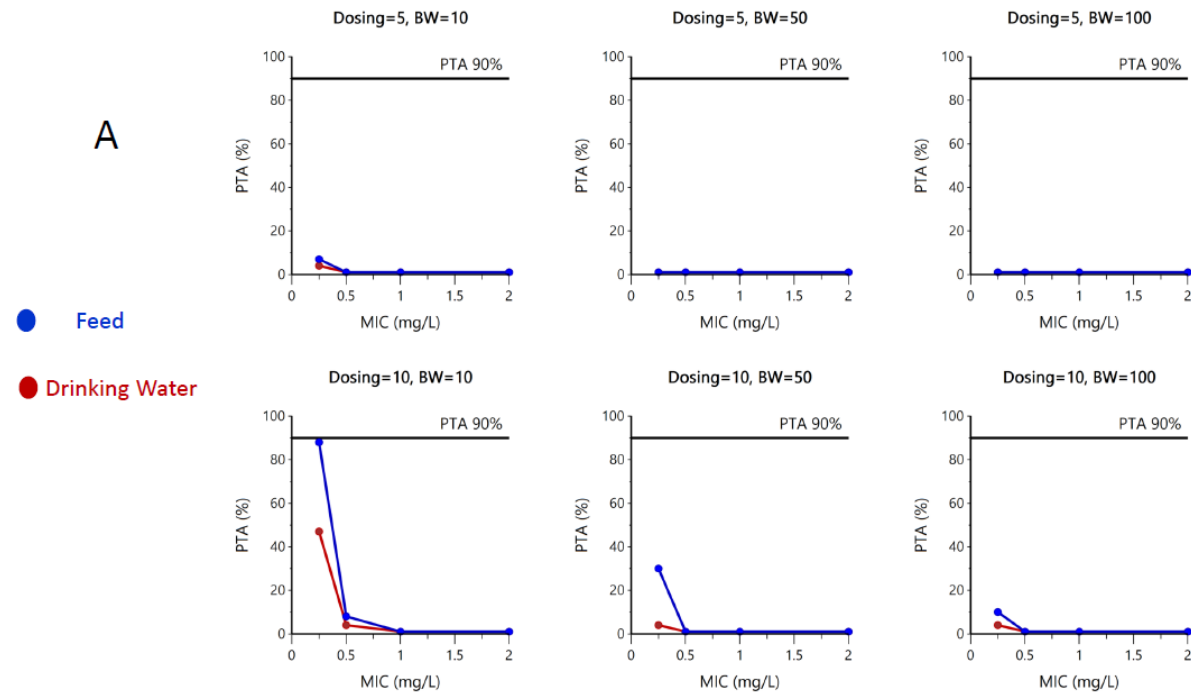


Figure 1. Plot of probability of target attainment for free plasma concentration AUC/MIC to remain above 24h, for all possible MICs, in steady state condition after administration of 5, 10 mg /kg (A) or 15, 20 mg/kg (B), for a 72h treatment.

The population PK model referred to in Section 5 was used to compute the Probability of Target Attainment for each possible MIC:

Clearance (Cl): 161, 259 and 320 mL/kg/h and Volume of Distribution (Vss): 1.08, 1.21 and 1.49 L/kg, for pigs of 10, 50 and 100 kg BW, respectively.

Fraction unbound (Fu): 31% ((Portugal et al. 2023)

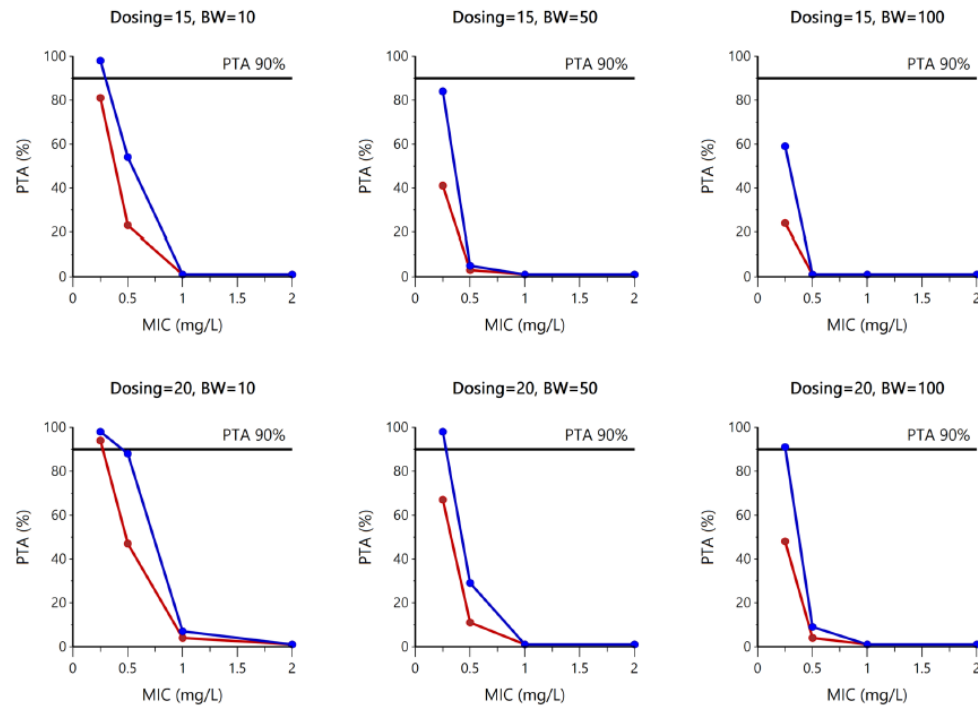
PK/PD index target (PDT): $AUC_{24h}/MIC > 24h$

The PTA curve corresponding to DOXY administered in feed and in field conditions is the purple blue
The PTA curve corresponding to DOXY administered by gavage in drinking water in laboratory condition the red curve



B

- Feed
- Drinking Water



The highest MIC for which it was possible to achieve a $fAUC/MIC \geq 24h$ for 90% of pigs was 0.25 mg/L in feed for a daily dose of 20 mg/kg regardless of body weight. The PK/PD cutoff approached 0.5 mg/L only in piglets of 10 kg BW and when DOXY is administered in feed at 20 mg/kg. For DW, only piglets of 10 kg BW were able to achieve a PK/PD cutoff of 0.25 mg/L with a dose of 20 mg/kg.

8. Clinical data

- No field trial data were submitted to support the use of DOXY in pigs during the registration process.
- In the only reported randomised, controlled, blinded study carried out in fattening pigs to assess the effectiveness of DOXY administered in the feed, it was demonstrated that an average dose of 11 mg/kg DOXY per day in feed for eight days was effective for metaphylactic control of pneumonia due to *P. multocida* and *M. hyopneumoniae* (Bousquet et al., 1998).
- Tentative efficacy of medication with DOXY in feed (about 10-12 mg/kg BW) in the control of pleuropneumonia in pigs was reported using an *A. pleuropneumoniae* aerosol challenge model (Luque et al. 2000).

References:

- Bousquet E, Pommier P, Wessel-Robert S, Morvan H, Benoit-Valièrgue H, Laval A. Efficacy of doxycycline in feed for the control of pneumonia caused by *Pasteurella multocida* and *Mycoplasma hyopneumoniae* in fattening pigs. *Vet Rec.* 1998 Sep 5;143(10):269-72. doi: 10.1136/vr.143.10.269.
- Luque I, Tarradas C, Carrasco L, Torroella E, Artigas C, Perea A. Effectiveness of doxycycline in the prevention of an experimental infection with *Actinobacillus pleuropneumoniae* in pigs. *J Vet Med B Infect Dis Vet Public Health.* 2000 Aug;47(6):445-51. doi: 10.1046/j.1439-0450.2000.00368.x.

9. Clinical breakpoints

	Age group	Organism group	MIC breakpoints (mg/L)		Notes
			S ≤	R >	
Species-related breakpoints	All weights	<i>Streptococcus suis</i>	0.5	0.5	.
		<i>Actinobacillus pleuropneumoniae</i>	-	-	Impossible to achieve sufficient exposure using oral treatment at recommended doses
	Piglets (up to 10 kg) weaning age	<i>Pasteurella multocida</i>	1	1	
		<i>Bordetella bronchiseptica</i>	1	1	
Species without breakpoints	<i>Glaesserella parasuis</i> ,		IE	IE	No CBP proposed as no ECOFF established yet
	<i>Mycoplasma hyorhinis</i> , <i>Mycoplasma hyopneumoniae</i>		IE	IE	No CBP proposed as no ECOFF established yet
Clinical qualifications	For administration of DOXY in feed formulations only.				
Dosage	Standard dose: 20 mg/kg of DOXY base in feed every 24h.				
Additional comments	For DW, experimental conditions modelled herein (gavage of starved pigs) are not predicting accurately field conditions, where pigs are having permanent access to water. Therefore, the CBPs are only applicable to the use of in-feed formulations. Pharmacodynamic analyses suggest that no breakpoints should exceed 0.25 mg/L, but this is based on studies of a single non-porcine species (<i>S. pneumoniae</i>) and therefore its general applicability is unknown. Instead, BP's have been set, where possible at the epidemiological cutoff values, which at least has the capacity to identify strains with likely acquired resistance mechanisms.				

10. Exceptions noted for individual national committees

None