Appendix:

PORCINE PREDICTION OF PHARMACOKINETIC PARAMETERS IN PEOPLE: A PIG IN A POKE?

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Drug Metabolism and Disposition

Methods used in data collection and selection of oral bioavailability data in pigs and humans:

All of the relevant published articles about the pharmacokinetics or bioavailability of drugs in pigs were obtained from a Pubmed search. The corresponding bioavailability data of those drugs in humans were obtained in the same way. Data were considered to be comparable on the basis of experimental conditions, including drug dose, drug dosage forms, human/animal fasted/fed status, *etc*. After examining the experimental methods and conditions under which the F values were determined, 31 pairs of F data were considered for analysis (Table A1). F refers to the absolute systemic oral bioavailability; by strict definition, both systemic PK (usually from an IV dose) and oral PK are needed to calculate absolute F. A few other considerations were made when evaluating the F for comparison.

- Food status should be the same in both pig and human. For example, food dramatically affects F of Fluoride. F in both pigs and humans was reduced by about 50% when the element was taken with food. Because food used in pigs and humans could not be compared, only the F values under fasted condition in both humans and pigs were used.

- If nonlinear elimination and/or absorption were observed, the comparison was made under the most comparable dose and/or exposure between the two species
- F may be calculated using other reasonable methods. For example, bioavailability of ciprofloxacin was calculated based on urine data (F = (Xupo×doseiv) /(Xuiv×dosepo)) was 48% (Xu is the amount of unchanged drug excreted in the urine for oral, po, or IV, intravenous administration).
- If absorption was known (such as from urine data) and no or minimal metabolism is involved in elimination, then F could be estimated based on the absorption fraction. Doxycline is an example of using urine data to calculate F.
- If complete absorption is verified and oral clearance is known, then F estimated by, Q/(Q+CLpo), was a reasonable method, such as for the case of levamisole (*Adams*, 1978); where Q is liver blood flow.
- If complete absorption was verified and hepatic clearance was estimated to be very low, indicating a low hepatic extraction ratio, then F was considered to be near complete and 95% F was assigned. This was the case for human F of sulphadiazine.
- If numerically F was reported over 100%, a 100% value was assigned.
- Some reported “F” values in pigs and humans were not included after
- careful examination of the reports for various reasons. Examples include:
    - In pigs, food administered differed significantly or unknown/incomparable in nature, such as for chloramphenicol, the

drug was co-administered with standard concentrate, milk or bran, which had no comparable experimental design in human studies (Bueno *et al.*, 1984).

- The AUC from intravenous dosing in humans was not available for griseofulvin, although the oral AUC/dose was comparable between pigs and humans (Aoyagi *et al.*, 1984).
- Urinary recovery of unchanged difloxacin was about 32% in humans after oral dosing, whereas in pigs, the AUC-based F was found to be 93.7% (Inui *et al.*, 1998; Granneman *et al.*, 1986).
- The plasma concentrations of quercetin after oral dosing in humans could not be detected, therefore, the F value for humans is not available (Ader *et al.*, 2000; Hollman *et al.*, 1995). The available data did not represent parent drug absorption and were considered unusable.
- Simultaneous dosing of five compounds (caffeine, warfarin, omeprazole, metoprolol and midazolam), which were dissolved and dosed in 10% w/v WellSolve at 1.0 mg/kg, were not included (Mogi *et al., 2012*). The total dose, combining five compounds, was actually 5 mg/kg. Comparing to solid dosage forms used in a human study, such oral dosages and forms may not be comparable. Potential precipitations in GI tract and potential interactions may occur as well. Midazolam F in pigs was only about 3%, comparing to ~12% in the

other study (Lignet *et al.*, 2016), raising the question of compatibility of this pig study to the studies in humans.

Table A1: Oral bioavailability values in pigs and humans.

Drugs	Breeds	F_{pig}	F_{human}	References
amoxycillin	Danish L-R×Duroc×Yorkshire	33	65	Agerso *et al.*, 1998; Paintaud *et al.*,1992
acetaminophen	Seghers Hybrid, Belgium	75.5	87	Rawlins *et al.*, 1977; Neirinckx *et al.*, 2010; Ameer, *et al.*, 1983
antipyrine	Göttingen Minipig	36	91	Vickers *et al.*, 1989; Lignet *et al.*, 2016; Rimmer *et al.*, 1986
chlortetracycline	Chester White×Yorkshire	15	30	Nielsen *et al.*, 1996; Kilrol *et al.*, 1990; Fabre *et al.*, 1971
cimetidine	Göttingen Minipig	33	78	Lignet *et al.*, 2016; Obach, *et al.*, 2008
ciprofloxacin	NA	37.3	48	Nouws *et al.*, 1988; Plaisance *et al.* 1987; Chukwuani *et al.,* 2000
cyclosporine	L-R	58	60	Mueller *et al.,* 1994; Primmett *et al.,* 1998; Keohane *et al.*, 2016
diclofenac	Yucatan miniature	100	42	Oberle *et al.*, 1994; Willis *et al.*, 1979
doxycycline	Conventional pig	100	95	Pijpers *et al.,*1994; Saivin *et al.*, 1988
fenofibrate	L-R	71	69	Zhu *et al.,* 2010; McCarthy *et al.,* 2017; Sauron *et al.,* 2006
finasteride	mixed breed (Hampshire, Yorkshire, and Swedish L-R	40	80	Lundahl *et al.*, 2011; Obach *et al.*, 2008
fluoride	Danish landrace	54.5	100	Richards *et al.*, 1982; Ekstrand *et al.*, 1979
hydrochlorothiazide	Göttingen Minipig	62	72	Sietsema 1989;

				Lignet *et al.*, 2016; Obach *et al.*, 2008
ketoprofen	L-R	86	85	Jamali and Brocks, 1990; Geisslinger *et al*., 1995; Neirinckx *et al.*, 2011
levamisole	Large-White	62	62.5	Watson *et al.*, 1988; Galtier *et al.*, 1983; Kouassi *et al.*, 1986
lincomycin	NA	73	63	Nielsen *et al.*, 1998; Simon *et al.*, 1976
lovastatin	Bama	4.97	5	Liu *et al.*, 2008; Obach *et al.,* 2008
meloxicam	Cross-bred Newsham cull sows	87	89	Turck *et al.*, 1997; Pairis-Garcia *et al.*, 2014
midazolam	Göttingen Minipig	12	34	Allonen *et al.*, 1981; Lignet *et al.*, 2016
moxifloxacin	Göttingen Minipig	54	82	Siefert *et al.*, 1999
naproxen	Danish land×York shire	91.6	74	Runkel *et al.*, 1972
oxytetracycline	NA	6	58	Nielsen and Gyrd-Hansen, 1996; Fabre *et al.*, 1971
pencillin V	NA	18.9	32	Nielsen and Gyrd-Hansen, 1994b; Bauer *et al.*, 1989
spiramycin	Swiss L-R	45.4	36	Sutter *et al.*, 1992; Frydman *et al.* 1988
sulfisoxazole	NA	100	100	Suber *et al.*, 1981; Kaplan *et al.*, 1972
sulphadiazine	NA	89	95	Nielsen and Gyrd-Hansen, 1994a; Reeves *et al.*, 1979
tetracycline	Chester White×Yorkshire	20.5	77	Kniffen *et al.*, 1989; Nielsen and Gyrd-Hansen, 1996; Fabre *et al.*, 1971
theophylline	Yorkshire	79	100	Tse *et al.*, 1982; Koritz, *et al.*, 1981; Boner *et al.*, 1987
trimethoprim	NA	90	100	Nielsen and Gyrd-Hansen, 1994; Chin *et al.*, 1995
vigabatrin	Göttingen Minipig	75	85	Nohr MK *et al.,* 2014;

Table A2: Systemic clearance (CL) values in pigs and humans

Drugs	Pig CL mL/min·kg	Human CL mL/min·kg	References
antipyrine	3.15	0.600	Lignet *et al.*, 2016
atenolol	7.95	1.00	Lignet *et al.*, 2016
cimetidine	37.4	8.30	Lignet *et al.*, 2016
diazepam	9.60	0.400	Lignet *et al.*, 2016
hydrochlorothiazide	11.8	3.00	Lignet *et al.*, 2016
midazolam	22.3	5.20	Lignet *et al*., 2016
theophylline	1.15	0.800	Lignet *et al.*, 2016
acetaminophen	3.18	5.00	Yoshimatsu *et al.*, 2016
antipyrine	3.94	0.640	Yoshimatsu *et al.*, 2016
atenolol	3.52	2.50	Yoshimatsu *et al.*, 2016
buprenorphine	17.1	18.9	Yoshimatsu *et al.*, 2016
diclofenac	1.20	3.50	Yoshimatsu *et al.*, 2016
felodipine	14.5	11.0	Yoshimatsu *et al.*, 2016
fentanyl	20.5	19.0	Yoshimatsu *et al.*, 2016
fexofenadine	4.74	3.10	Yoshimatsu *et al.*, 2016
flurbiprofen	0.790	0.300	Yoshimatsu *et al.*, 2016
furosemide	5.75	1.60	Yoshimatsu *et al.*, 2016
ketoprofen	0.913	1.14	Yoshimatsu *et al.*, 2016
lidocaine	12.8	13.6	Yoshimatsu *et al.*, 2016
propranolol	11.1	12.0	Yoshimatsu *et al.*, 2016
raloxifene	21.5	10.8	Yoshimatsu *et al.*, 2016
caffeine	0.966	1.40	Mogi *et al.*, 2012
warfarin	0.139	0.055	Mogi *et al.*, 2012
omeprazole	8.44	8.40	Mogi *et al.*, 2012
metoprolol	26.7	13.0	Mogi *et al.*, 2012
midazolam	13.9	5.30	Mogi *et al.*, 2012
finasteride	7.00	2.40	Lundahl *et al.*, 2011 Steiner 1996
amoxycillin	9.67	3.30	Reyns, 2007; Obach *et al.*, 2008
ciprofloxacin	17.5	8.30	Nouws *et al*, 1988; Obach *et al.*, 2008
doxycycline	1.67	0.460	Zhang *et al.*, 2018; Obach *et al.*, 2008
lincomycin	6.83	2.10	Kurohad, *et al.*, 2001
moxifloxacin	10.8	2.40	Siefert *et al.*, 1999; Obach *et al.*, 2008

tetracycline	3.08	1.50	Nielson and Gyrd-Hansen, 1996; Obach *et al.*, 2008
sulphadiazine	2.33	0.550	Nielson and Gyrd-Hansen, 1994; Obach *et al*., 2008
sulfisoxazole	4.41	0.300	Obach *et al.*, 2008; Suber *et al.*, 1981;
trimethoprim	9.17	2.10	Nielson and Gyrd-Hansen, 1994; Obach *et al.*, 2008
cyclosporine	8.95	7.50	Vaden and Riviere, 1990; Obach *et al.*, 2008
ketamine	48.1	19.0	In-house
meloxicam	0.718	0.120	Pairis-Garcia *et al.*, 2014; Obach *et al.*, 2008
lovastatin	22.6	7.20	Liu *et al.*, 2008; Obach *et al.*, 2008

References for Appendix Table A1 (oral bioavailability in pigs and humans):

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