Institution: Royal Veterinary College
Unit of Assessment: A 6 Agriculture, Veterinary and Food Science
Title of case study: **Optimising antimicrobial drug use for efficacy, safety and avoidance of resistance**

1. Summary of the impact (indicative maximum 100 words)

Dose selection for antimicrobial drug (AMD) use is fundamentally important in avoiding the emergence and subsequent spread of antimicrobial resistance (AMR), as well as for ensuring a successful clinical outcome. RVC's pioneering research and expertise in pharmacokinetic/ pharmacodynamic (PK/PD) integration and modelling for veterinary applications has introduced a novel, rigorous scientific method to dosage regimen design, which has been implemented in veterinary AMD registration, guiding national and international licensing authorities. Work on AMD dosages for livestock species, frequently undertaken in collaboration with industry, has contributed substantially to this understanding and consequent changes in drug registration practices worldwide.

2. Underpinning research (indicative maximum 500 words)

Since 1998 the integration and modelling of pharmacokinetic and pharmacodynamic data have been applied to the prediction of safe and effective drug dosages for AMDs, not merely to give a clinical cure but providing a bacteriological cure and minimising risk of resistance emerging. Peter Lees (Professor of Pharmacology, Emeritus from 2004) has made a significant contribution to this research in the veterinary field, with reference to effective AMD usage, whilst minimising the risk of emergence of AMR. The work developed at RVC has been facilitated by collaboration with Professor Pierre-Louis Toutain of the French National Veterinary School at Toulouse (Visiting Professor of the RVC 2008-10).

Initial studies conducted in vitro, ex vivo and in vivo established the PK/PD paradigm for dosage selection of AMDs [1]. This led to the generation of dosage proposals for marbofloxacin in calves. Subsequently, work involving another fluoroquinolone, danofloxacin, generated similar data for sheep [2]. This work clearly demonstrated that fluoroquinolones exhibit a concentration-dependent killing effect against field strains of veterinary pathogens in biological fluids. PK/PD modelling approaches have since been critical in demonstrating the in vivo efficacy of fluoroquinolone drugs, and have been responsible for key revisions in registered dosage regimens. Lees extended his work on ex vivo pharmacodynamic data involving relevant veterinary pathogens modelled with in vivo pharmacokinetic data to in vivo PK/PD modelling, using an experimental model of calf pneumonia relevant to clinical use (in collaboration with the Moredun Research Institute and Pfizer Animal Health (now Zoetis)). A landmark paper on danofloxacin [3], showed the concentration-dependent killing action of danofloxacin in pneumonic calves and collaboration with Pfizer Animal Health led to a pronounced revision of the dosage schedule from 1.25 to 6.0 mg/kg to optimise treatment based on this understanding. The same principles are now being applied by RVC researchers, with BBSRC CIDLID funding, to contagious bovine pleuropneumonia in Kenya with the goal of informing optimal AMD dosing to tackle this intractable health problem in indigenous cattle [4].

Because of the importance and clinical relevance of Lees's early studies, DEFRA commissioned him to undertake a four year programme in 2006 to examine dosing regimens for five classes of AMDs used in the treatment of calf pneumonia. This programme involved a comprehensive and progressive approach, starting with *in vitro* and *ex vivo* pharmacodynamic studies conducted in biological fluids [5], PK/PD modelling informed by tissue cage experiments in healthy calves [6] and by an experimental disease model (calf pneumonia) [7,8], population pharmacokinetics of tulathromycin in field cases of calf pneumonia, and Monte Carlo simulations to propose optimal dose rates [7,8]. His data challenged the conventional approach of using artificial media in studies of AMD potency, and demonstrated distinct differences in pharmacokinetic profiles of AMDs between infected and healthy calves; such differences, if known, can be allowed for when

evaluating dosage regimens for novel agents. Of particular relevance to AMR, the studies demonstrated how readily relatively stable resistance can arise following administration of a single therapeutic dose (recommended on the label) – by persistence of partial resistance at four weeks to tulathromycin in enterococci and Escherichia coli harvested from calf faeces. [7,8]

The use of a population pharmacokinetic approach with limited sampling analysed by Monte Carlo simulation added to the data obtained *ex vivo*, and coupled with an *in vivo* challenge model has set the gold standard for future research and development of AMDs for veterinary medicine.

His report to DEFRA demonstrated the major deficiencies of the conventional dose-titration approach to dose selection, which generally leads to a clinically effective dose but one which is sub-optimal in achieving bacteriological cure [8].

Further quality indicators

Lees has received many awards of international standing, including the Selbourne Award of the Association of Veterinary Teachers and Research Workers in 2004 and the Lloyd E Davis Award of the American Academy of Veterinary Pharmacology and Toxicology, for lifetime achievements in veterinary pharmacology, in 2007.

P Lees. Minimising the emergence of resistance to antimicrobial drugs through rational dosage schedule design based on pharmacokinetic-pharmacodynamic (PK-PD) modelling and population PK-PD modelling. Defra. 2006-10. £336,500.

3. References to the research (indicative maximum of six references)

1. Shojaee AliAbadi, F, Lees, P. 2002 Pharmacokinetics and pharmacokinetic/pharmacodynamic integration of marbofloxacin in calf serum, exudate and transudate. Journal of Veterinary Pharmacology and Therapeutics; 25: 161-174 DOI: 10.1046/j.1365-2885.2002.00399.x

2. Aliabadi, FS, Landoni, MF, Lees, P. 2003 Pharmacokinetics (PK) Pharmacodynamics (PD) and PK-PD Integration of Danofloxacin in Sheep Biological Fluids. Antimicrobial Agents and Chemotherapy; 47: 626-635 DOI: 10.1128/AAC.47.2.626-635.2003

3. Sarasola, P, Lees, P, AliAbadi, FS, McKellar, QA, Donachie, W, Marr, KA, Sunderland, SJ, Rowan, TG. 2002 Pharmacokinetic and Pharmacodynamic Profiles of danofloxacin administered by two dosing regimens in calves infected with *Mannheimia (Pasteurella) haemolytica.* Antimicrobial Agents and Chemotherapy; 46: 3013 – 3019 DOI: 10.1128/AAC.46.9.3013-3019.2002

4. Mitchell JD, McKellar QA, McKeever DJ. 2013 Evaluation of antimicrobial activity against Mycoplasma mycoides subsp. mycoides Small Colony using an in vitro dynamic dilution pharmacokinetic/pharmacodynamic model. J Med Microbiol. 2013 Jan;62(Pt 1):56-61. doi: 10.1099/jmm.0.045971-0.5.

5. Illambas, J, Potter, T, Cheng, Z, Rycroft A, Fishwick J, Lees P. 2013 Pharmacodynamics of marbofloxacin for calf pneumonia pathogens. Research in Veterinary Science; 94675-681. DOI:.org/10.1016/j.rvsc.2012.12.012

6. Potter, T, Illambas J, Pelligand, L, Rycroft, A, Lees, P. 2013 Pharmacokinetic and pharmacodynamic integration and modelling of marbofloxacin in calves for Mannheimia haemolytica and Pasteurella multocida. Veterinary Journal; 195:53-8. DOI: 10.1016/j.tvjl.2012.08.027

7. Potter, T. 2011 Pharmacokinetics and pharmacodynamics of antimicrobial drugs used in the treatment of calf pneumonia. PhD thesis. Royal Veterinary College, University of London

8. Report to Defra http://randd.defra.gov.uk/Default.aspx?Menu=Menu&Module=More&Location=None&Completed=2&ProjectID=14235

4. Details of the impact (indicative maximum 750 words)

AMR is a long-standing and escalating problem in both human and veterinary medicine. In addition, it is now well recognised that one may impact upon the other. For example, cross-resistance to fluoroquinolones used in human treatment may be caused by veterinary use of a drug of the same class. Fluoroquinolones have applications as easy-to-use first or second-line therapeutics for intractable systemic infections, with major herd health implications in food-producing animals. Consequently, it is important economically and from an animal welfare perspective to maintain their efficacy through prudent use and dosage optimisation. In 2008, 2

tonnes of fluoroquinolones were used in food production animals in the UK, from a total of 384 tonnes of therapeutic AMDs.

Following a rise in human fluoroquinolone-resistant Campylobacter infections in the USA, possibly associated with consumption of poultry, in 2005 the FDA withdrew approval for use of enrofloxacin in poultry. This was a seminal event:- the first time an animal drug had been removed from sale because of potentially associated emergence of resistance in humans. It led to subsequent drug evaluation using a system that focused on probability of AMR emergence and, specifically, the probability of that resistance transferring to human infectious disease therapy – particularly for drugs such as fluoroquinolones - that are essential for treatment of life threatening infections in both humans and animals. In Europe, regulatory authorities have taken a similar approach [a].

Through his published research and direct advocacy, Lees has contributed substantially to these changes in veterinary drug registration practice: both the FDA and the European Medicines Agency (EMA) now emphasise the importance of PK/PD modelling to establish doses that eradicate the bacterial infection as well as providing a clinical cure.

The 2006-2010 Antimicrobial Strategy of the EMA Committee for Medicinal Products in Veterinary Use (CVMP) noted "… possibilities to further use PK-PD modelling in the establishment of best dose and dosing regimen" [b]. Their Strategy on AMDs for 2011 – 2015 focuses strongly on the importance of measures to minimise risks from AMR. However, in reviewing the previous strategy document it notes that PK-PD modelling had only been addressed at a product level, rather than being adopted in revised general guidance [c]. The revised Guideline has now been produced, which states where PK/PD relationships are well established "… it may be possible to omit dose-determination studies" and run clinical trials testing one or a very few regimens [d]. Consequently, Lees's work and advocacy has also made a contribution to animal welfare through a reduction in experimental animal use.

Lees has been instrumental in providing guidance and ensuring implementation of this integrated PK/PD approach. The Office for New Animal Drug Evaluation at the Center for Veterinary Medicine, US Food and Drug Administration acknowledges this [e]: "Dr Lees has served as a source of invaluable contributions to the body of knowledge impacting the development and use of veterinary pharmaceuticals. From an informational perspective, the community of veterinary clinical pharmacology experts have a far greater understanding of pharmacokinetics (PK), interspecies differences, and exposure-response relationships (PK/PD) through his published works." The Head of Veterinary Medicines and Product Data Management at the EMA also recognises this contribution [f]: "Recognising that the production of scientific papers alone is often insufficient in itself to change regulatory practice, Professor Lees has been a vocal advocate for the integration into regulatory guidance of the principles supported by his research." This has included delivery of invited seminars to assist in up-skilling members of regulatory bodies and policy makers. These presentations have focussed on both improving understanding of the application of PK/PD modelling to optimise dosage selection for avoiding AMR, and on effective drug registration policies to minimise AMR in production animal and human medicine. Lees presented to the CVMP's annual symposium in 2005 and 2008. In 2011, he delivered a series of similar presentations for members of Defra and the Veterinary Medicines Directorate (VMD). Through his position as a Council member of the Royal College of Veterinary Surgeons, Lees has contributed to the formal 'Technical Engagement' for the next UK five year Antimicrobial Resistance (AMR) strategy and action plan, which the Department of Health has been developing in collaboration with Defra [g].

Lees's PK/PD integration/modelling approach has been disseminated, and its uptake by industry advanced, through conventional publication and conference presentations, including invited plenary lectures at major conferences for the scientific, regulatory and veterinary communities, such as the European Association for Veterinary Pharmacology and Toxicology Congresses, 2009 and 2012. He has been a member of all organising committees of: the bi-annual International Congresses on Antimicrobial Agents in Veterinary Medicine since 2002 and the tri-annual European Association for Veterinary Pharmacology Congresses since 1988.

The move towards assessment of drug approvals based on AMR risk alongside clinical benefit has, of course, been mirrored by changes in industry research and development, to assemble data that meet the regulators' requirements. Lees has undertaken much of his work in collaboration with animal health companies, demonstrating selection of optimised treatment regimens through PK/PD modelling. To gain and preserve their market approvals, animal health companies are keen to show that, prudently used at an appropriate dose rates, their drugs will minimise AMR risk. For safe and practical field application they need to balance selection of higher dosages to ensure bacterial eradication against possible host toxicity and economic viability, with regard to the cost of the treatment [h].

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5. Sources to corroborate the impact (indicative maximum of 10 references)

a. EMA information on AMR and antimicrobial drug registration etc.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000439.jsp&mid=WC0b01ac058002d4e9 [accessed 5 Mar 2013]
b. 2006-10 strategy document 2006 (Pages 3 and 9 of 16)
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/10/WC500005154.pdf
[accessed 29 Oct 2013
c. 2011-15 strategy document 2011 (Page 11 of 12)
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/07/WC500109137.pdf
[accessed 29 Oct 2013]
d.New Guideline document 2013 (still in consultation) (Pages 6-7 or 14
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/05/WC500143698.pdf [accessed 29 Oct 2013]
e. Statement from officer of the Office for New Animal Drug Evaluation at the Center for Veterinary Medicine, US Food and Drug Administration, held at RVC.
f. Statement from Head of Veterinary Medicines and Product Data Management, EMA, held at RVC.
g. RCVS consultation response to DOH 'Technical Engagement' request regarding new 5 year antimicrobial resistance strategy and action plan. Held by RVC.
h.Comparison of Advocin (single dose, short withdrawal period) with Baytril.
https://online.zoetis.com/us/en/products/pdf/advocin_reference%20final%202%2022%2012%20(2).pdf [accessed 5 Mar 2013]
i. FOI summary on advocin formulation at 8mg
http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/UCM292024.pdf [accessed 5 Mar 2013]
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