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ANTIMICROBIAL PRODUCTS IN THE 21ST CENTURY: OPTIMAL USE AND CLINICAL DEVELOPMENT

Lloyd Reeve-Johnson*
School of Veterinary Science, University of Queensland

SUMMARY

The success or failure in the marketplace of a novel antimicrobial product represents a financial risk on the part of a pharmaceutical company that is underpinned by the rationale of a scientific approach to its development. There are a variety of financial, marketing and pharmacological models that can be used to make predictive assessments of likely product success and the financial implications. The paper discusses development and use of antimicrobials and proffers suggestions of what constitutes optimal use by veterinary practitioners who through their role as dispensers of prescription products are by default the gatekeepers to the animal health market and share responsibility for the financial success or failure of veterinary products.

Keywords : Antimicrobial development, economic modelling, antimicrobial efficacy, dosage regimes

INTRODUCTION

Repeated use of antimicrobial products by veterinary practitioners is generally based upon their experience of clinical effectiveness in previous similar situations. During the clinical development of antimicrobial products, marketing authorisation in most countries is partly dependent upon the demonstration of clinical efficacy. Clinical assessments are utilised to confirm preferred dosage regimes. These 'Phase 3' clinical studies are generally the most costly phases of development for new products (Reeve--Johnson, 2003a). The variability in clinical cases, difficulty in obtaining sufficient numbers of cases within a restricted timeframe and subjective assessments based upon clinical signs rather than the objective pathological measures generally restrict clinical studies to a dose confirmation rather than a dose development role. The dosage regime is usually determined by modelling the disease and treatment scenarios under controlled situations and utilising pharmacokinetic and pharmacodynamic parameters to justify the rationale (Reeve-Johnson, 1998). The inability of a clinical trial to distinguish a good from a bad antibiotic has been frequently illustrated; generally this is due to the design of studies which establish equivalency of effect, but do not have sufficient patient numbers under consistent conditions to demonstrate statistically valid superiority to another product (Dagan *et al.*, 2001).

Clinical trial work has been demonstrated in both human and animal patients to be not sensitive enough to establish a dosage regime that guarantees total bacterial cure. In many cases the clinical objective should be to establish a total bacterial cure, if bacterial eradication does not occur, less susceptible bacteria are likely to lead to the re-colonisation process after the cessation of therapy and a more resistant population of bacteria will become predominant. The situation has been described by several sources, whereby if antibiotic efficacy is measured by the reduction in clinical signs, drugs or dosing regimes with excellent antibacterial activity will not appear as effective as anticipated while the opposite will occur for antibiotics with poor antibacterial activity. For example, Marchant *et al.* (1992) studying otitis media in children showed that when 100% bacterial eradication is achieved, the clinical success rate may only be 89%, yet with a placebo typically 27% bacterial cure was attained via the host natural defence mechanisms and a clinical success of 71 % was still attained. An example of the inconsistency of matching *in vitro* pharmcodynamic data and pharmacokinetic data with clinical outcome was encountered in pigs where a macrolide antibiotic of low *in vitro* efficacy was found to be highly effective in the clinical patient. It was shown using immuno-contrast staining techniques that the antibiotic accumulated in the primary alveolar macrophages of the lung and whilst the Minimum Inhibitory Concentration (MIC) data and blood concentration data indicated that the product would be relatively ineffective, the concentration of the drug was found to be approximately 75x the MIC value at the localised site of activity in the body (Reeve-Johnson, 1998; 2000a).

In another study the clinical and pathological data were correlated and it was found that with pigs infected with *Actinobacillus pleuropneumoniae* the ante-mortem clinical presentation often bore no correlation at necropsy with the pathology occurring within the lungs of severely diseased pigs and that the strain of the infecting bacteria and endotoxin release had a large affect on the clinical signs observed. Severely ill pigs with peracute disease would present on necropsy with little gross pathological

* Recognised European Specialist in Veterinary Pharmacology
Professor of Veterinary Pharmacology, Head of School of Veterinary Science, University of Queensland

evidence of disease while substantial abcessation was found in pigs with few clinical signs (Reeve-Johnson, 1999a; 1999b). When assessing the effectiveness of an antimicrobial product, it is therefore important that relevant, objective and measurable endpoints are chosen as the desired outcome from treatment in advance of initiation of treatment. A further consideration in food producing animals is ensuring accountability for residues of drugs and metabolites in edible tissues such as meat, other body organs, milk and eggs. The pharmacokinetic characteristics determine the concentrations to which a drug distributes within the body at the subcellular, tissue and organ levels. The ideal scenario is a drug of the appropriate activity spectrum which distributes at therapeutic concentrations to the intended sites of activity but not elsewhere, minimising the total dose needed.

The practitioner is concerned primarily with obtaining a clinical cure, but this may be only temporary and unless methodical case follow up at the end of treatment is routinely done, the proportion failing to achieve bacteriological cure will not be evident and lack of attaining complete cure selects for a remaining population of bacteria which are inherently more resistant to the drug being used. Antibacterial activity can be both time and concentration dependent, thus delivering the right dosage regime and comparing the results against the desired outcome provides an evidence-based approach for practitioners to evaluate the way they use antibiotics under practical conditions. The remainder of this paper will deal with aspects under the themes of product development and product use:

Product development:
1. The context of the veterinary market for drug development
2. Deciding upon the requirements of the drug
3. Pharmacodynamic and pharmacokinetic predictors of drug efficacy

Product use:
1. The function of the clinical study
2. The way the use of a product is influenced by the market
3. Optimising use of antimicrobials

PRODUCT DEVELOPMENT

The context of the veterinary market for drug development

The animal health market was valued in 2004 at USD12 545 million which translates to USD12 000 million in 1995 and USD11 330 million in 2002. The market is relatively stagnant representing a growth of under 5% over a 10-year period. The market has changed dramatically in the way it is segmented during this period. A point to note is the companion animal sector which has increased from 22% to 38.5% of the total market value at the expense of all other sectors (Figure 1). Another reality is the very small share of the global animal health market represented by Australia (that is, well under 3% of the global market in comparison to 36% in the USA and 29 % in the EU). Unless Australian research can demonstrate its applicability to the global marketplace and offer high

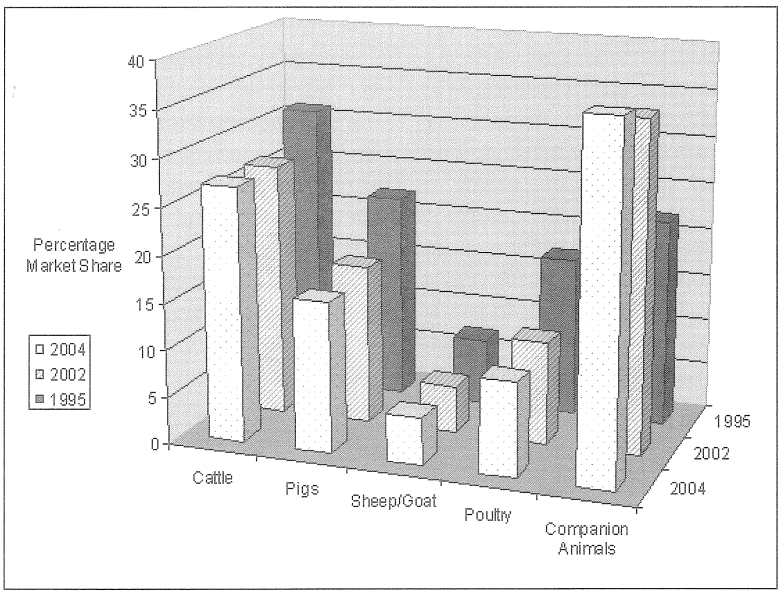

Figure 1: Global animal health market trends 1995, 2002, 2004. Total value estimated was USD12,000 million in 1995, USD11,330 million in 2002, USD12,545 million in 2004

Table 1 : Two way table illustrating the preference of uptake of health care procedures and products based on criteria of treatment cost and efficacy (1= most desirable and 4= least desirable)

		Efficiency of Treatment	
		High	Low
Cost of Treatment	High	2	4
	Low	1	3

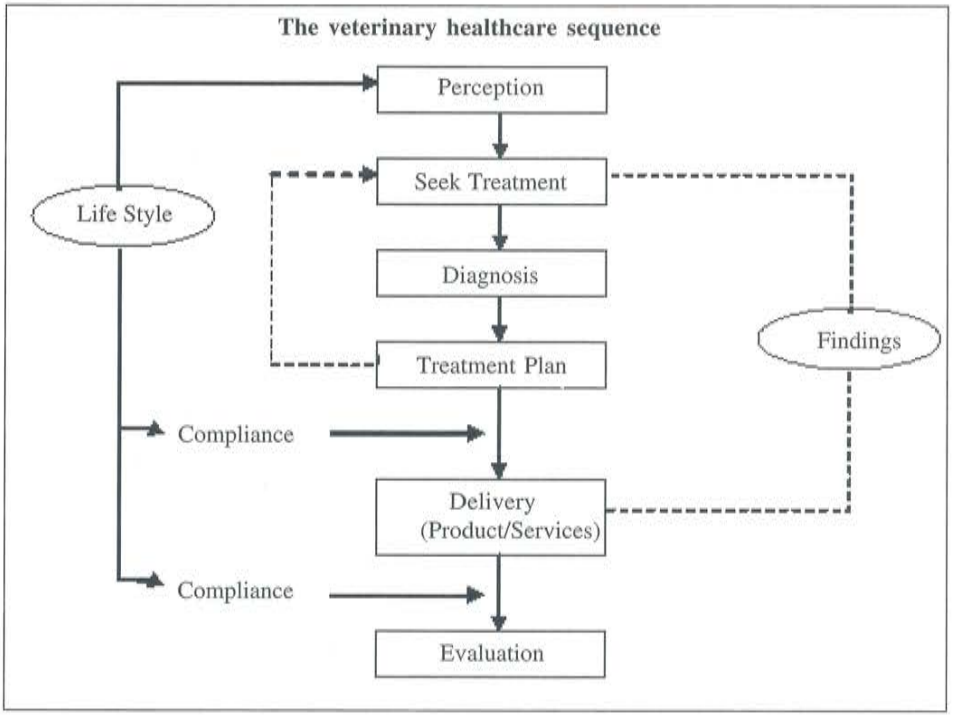

Figure 2: modelling approach

quality research at a competitive cost, there is be little incentive for internationally based animal health companies to consider investing or developing products in Australia.

Veterinary healthcare provision can be described as a transaction, in which there are a small number of identifiable participant groups which have a large influence on the size of the market and the commercial viability of individual products (Reeve--Johnson, 2003b). One of the fundamental choices that the veterinarian dealing with clients in a commercial situation is faced with is balancing the desire for highly effective treatment with an affordable cost. Table 1 illustrates the usual market preference between the segments available. While low cost, high efficacy is the preference, the reality is often deciding whether the price or efficacy need to compromise (that is, segments 2 and 3). The perception by the veterinarian and the client of a product's efficacy and price actually determines into which segment it will be categorised. This reflects the 'value' of the product in the market. The basic sequence of health care provision is presented in Figure 2. Progression through each stage is affected by access to information for the owner and veterinarian and access to other resources which are ultimately constrained by affordability as well as the implications that the treatment plan will have upon the lifestyle of the owner and the patient, which affects the level of compliance.

Deciding on the requirements of the drug

Before a drug can be used, there needs to be a clear decision as to the intended outcome needed in terms of the therapeutic effect and toxicological profile. Each drug has unique distribution, activity and toxicity profiles which determine the most rational choice of drug and dosage regimens. When considering antimicrobial use, most pathogens of clinical interest are located extracellularly, therefore the biophase for antibiotics is the extracellular fluid (ECF). Except for plasma, ECFs are difficult to sample; however, if there is no barrier to impede

diffusion of the drug, the concentration of the unbound drug in the plasma approximates the concentration of unbound drug in the ECF. In contrast, where there is a barrier to diffusion (for example, Central Nervous System, eye, prostate etc) the plasma concentration is much less useful. Similarly, the relationship between the plasma concentration and the ECF may be altered substantially by changes in blood supply which may increase the local concentration when there is inflammation or decrease the local concentration when there is reduced blood flow, for example, inflammatory tissue and debris, sequestered bone fragments, shock or cardiac or renal insufficiency.

Lipid solubility and binding to carrier mechanisms play a more important role where there are barriers to diffusion and in cases of intracellular infection some drugs have been demonstrated to penetrate cells to different levels, that is, beta-lactams (penicillin, ampicillin, cephlasporins) diffuse into but do not accumulate in phagocytes; aminoglycosides (gentamicin, neomycin, streptomycin) are taken up slowly into cells by endocytosis; macrolides (erythromycin, tylosin, tilmicosin) localise in the cytoplasm and lysosome while fluoroquinolones diffuse into cells and accumulate in phagocytes. However, the most important aspect of maintaining clinical effectiveness is having an adequate host defence mechanism and while the objective may be to eliminate infection, without an adequate host response, partial cure or reinfection should be anticipated. The case of macrolide antibiotics work has demonstrated that there are a number of potentially advantageous immunomodulatory effects (Labro, 1993). The selective modulation of the host immune response in conjunction with effective antimicrobial treatment remains a largely unexplored area for research and offers hope in the face of increasing levels of antibiotic resistance.

Once the target of activity (that is, bacterial species), location within the body (systemic, organ, cell) and appropriate treatment outcome have been defined (that is, antimicrobials act on infectious organisms not on clinical signs), pharmacodynamic and pharmacokinetic techniques can be used to predict the clinical efficacy.

Pharmacodynamic and pharmacokinetic predictors of drug efficacy

The relationships between antibiotic exposure, rate of bacterial killing and possible bacterial regrowth can be investigated with *in vitro* systems modelling the expected *in vivo* concentration profiles in the target species (Murakawa *et al.*, 1980). These models have been used to determine the pharmacokinetic parameters, but the limitation is that they do not take account of the role of the immune system of the host. Pharmacodynamic measures of *in vitro* efficacy need to be combined with pharmacokinetic work to account for *in vivo* distribution effects such as the plasma binding and lipid solubility of different classes of antibiotics. In the case of aminoglycosides, and some of the fluroquinolones plasma binding is low and the measured plasma concentration may be considered to be similar to the ECF concentration, conversely as the amount of protein binding increases a correction for binding is needed. It should also be noted that the free concentration is controlled by the drug clearance from the body primarily by the liver and kidney. There are clearly differences in clearance in individual patients for which even the most refined pharmacokinetic model could not cater.

The most frequently used pharmacodynamic indicator of efficacy is the Minimum Inhibitory Concentration expressed generally as an MIC_{90} (the minimum amount of drug required to inhibit growth of 90% of the strains tested). One disadvantage is that it is established as doubling dilutions meaning that an inaccuracy of 100% is built into the system. A second point to remember is that inherently a sub-population of 10% of strains in the population which are less susceptible are a potential source of future resistance in the population. For this reason, authorities governing product registration generally stipulate that the antimicrobial dosage regimes should attain a plasma concentration of at least twice the MIC_{90} and that the concentration should be greater than the MIC_{90} for at least 50% of the inter-dose interval. It could be argued that for time dependent antibiotics (for example, beta-lactams, cotrimoxazole or macrolides), this is an absolute minimum time to maintain drug levels above the MIC_{90}. However, in the case of concentration dependent antibiotics, much higher concentrations at the site of action are warranted (for example, aminoglycosides and fluoroquinoloines). Some antibiotic drugs accumulate at the site of infection, for example, due to concentration and transport in phagocytic cells or due to altered pH gradients during infection, thus the concentrations at the site of activity can be several times the ECF concentrations. This phenomenon may be responsible in part for the post-antibiotic effects and sub--MIC effect recorded for some of the macrolides, fluoroquinolones and aminoglycosides.

In general, a safe rule within the bounds of the toxicological profile is to aim for concentrations which are maintained above the MIC_{90} for over 75% of the inter-dose interval. A peak concentration above twice the MIC is often needed to sustain this kinetic profile. For concentration-dependent drugs, a concentration (C_{max}) of twice the MIC should be regarded as a minimum. If the MIC of the bacterial pathogen is obtained by the clinician, this can be easily compared with the distribution levels for the recommended dose provided by the manufacturer.

PRODUCT USE

The function of the clinical study

The clinical study is used to validate the efficacy as predicted by *in-vitro* and disease modelling techniques under practical conditions within a varied patient population. It is also the first step in the pharmacovigilance process whereby adverse event reporting is initiated. A fundamental component of clinical study design should be to ensure that the clinical signs being recorded as indicative of a pathological disease process (for example, rectal temperature, clinical score, demeanour) are sufficiently objective measures. The measures used to assess clinical success must be clearly related to the treatment objective (for example, lowering clinical temperature is not the objective in treating pneumonia in cattle and pigs; the objective is eliminating infection and restricting lung damage). For example, it has been found that rectal temperature is a very good surrogate and has a strong positive correlation (p=0.05) with lung damage, bacterial infection and clinical condition in mildly diseased calves infected with Pasteurella and Mycoplasma *spp*, but in severe disease homeostasis is compromised and the correlation no longer exists (Reeve-Johnson, 1999b; 2001). In a separate work, it was also found that the magnitude of diurnal variation in calves housed outdoors can be greater than the variation in rectal temperature due to disease depending upon the time of day that the measure is taken (Reeve-Johnson, 2000b). In the case of *Actinobacillus pleuropneumonia* infections in pigs, there was found to be no reliable correlation between rectal temperature, clinical demeanour, respiratory signs, lung to body-weight ratio or chronicity or number of colony forming units isolated from the bacterial infection (Reeve-Johnson, 1999a). This author has been involved in the review of registration dossiers for new product licences, which routinely claim clinical effectiveness for their antimicrobial products based upon decreases in rectal temperature when treating swine pneumonia. The message is that the desired treatment end point is the most appropriate measure; this should relate to the spectrum of the antibiotic activity and surrogate measures should be substantiated and used with extreme care as they can be misleading.

The way the use of a product is influenced by the market

The utilisation of a product by the market is part of a sequence of events that may or may not occur depending on a decision as to what course of action to take at each point. Simplistically, the client has to decide to seek treatment for their animal; they then have a choice from whom they seek treatment. If this is a veterinarian, the level of testing in support of a diagnosis, their knowledge of the range of pharmacological treatment options available and previous clinical experience are likely to influence the choice of antibiotics. The compliance of the client and ensuring an effective duration of treatment will be affected by the veterinary clinician's policy on re-checking cases and the combination of subjective clinical and other objective testing (for example, blood biochemistry, haematology or bacterial culture) performed to validate that the appropriate end point of treatment has been reached. Client compliance is influenced by the level to which they are aware of the consequences of non-compliance and their understanding of the relevance of the endpoint of treatment (Reeve-Johnson, 2003b). This combination of factors has a very large influence on channelling the patient towards the appropriate treatment and therefore the market size for that drug. Figure 3 illustrates how this works if all options are set an equal

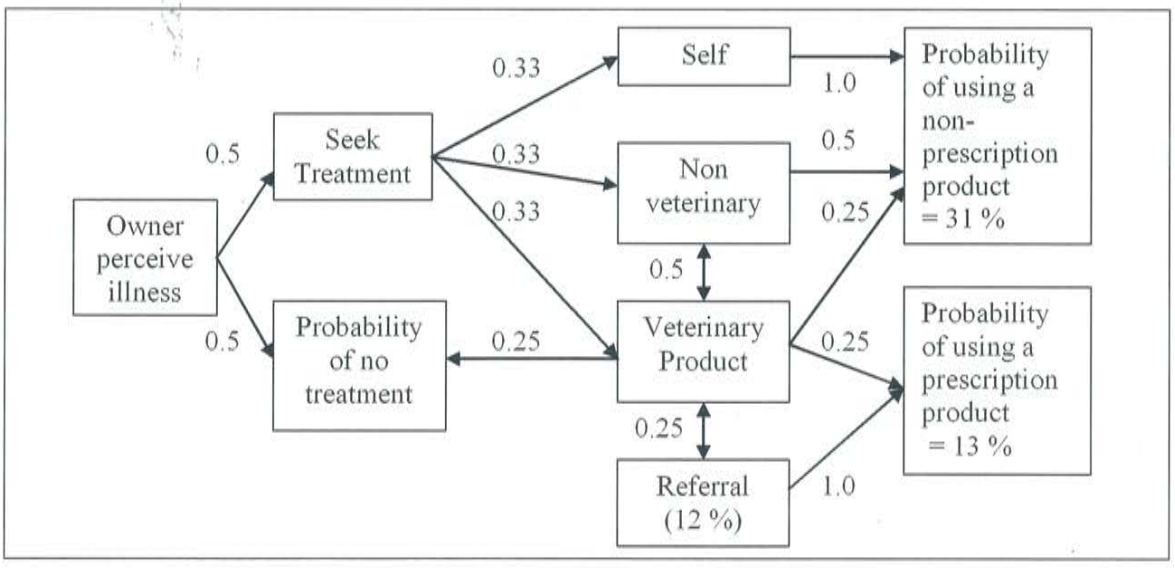

Figure 3: Worked example of a decision cascade from the point of perception of illness through to dispensing of therapy (theoretical example where the probability of all decisions is set as equal)

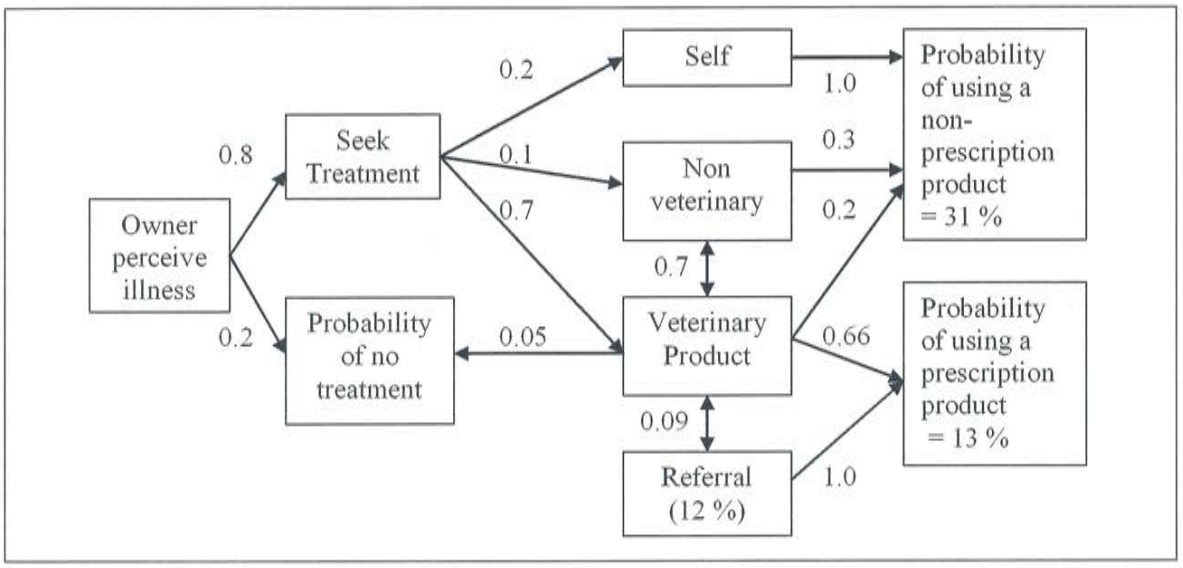

Figure 4: Worked example of a decision cascade from the point of perception of illness through to dispensing of therapy using data from our practice

probability of occurring, the probability in this theoretical example is that 13% of cases would get a prescription product. Figure 4 uses actual data from a large group of companion animal veterinary practices in the United Kingdom and shows how the influence of marketing, education and evidence of therapeutic success provide information to the client and the practitioner and have changed the proportion of prescription products used to 46 % as well as improved compliance and duration of treatment (Reeve-Johnson, 2003a; further data in press).

The initiator of the entire veterinary healthcare transaction is the owner who needs to have the knowledge to make the decision to seek treatment based upon signs in the animal and then to approach a veterinarian out of preference. The veterinarian is the gatekeeper for the prescription process for antimicrobial products and the choice of product is based upon their knowledge of the available options and the past experience. These decisions determine the ultimate size of the market and extent to which products are utilised. It is a duty therefore to ensure as veterinarians that our decisions are evidence based and that we have data to support our choices and the way we influence the market.

Optimising use of antimicrobials

Veterinarians have been granted the privilege of dispensing prescription drugs, which infers responsibility. This responsibility obliges clinicians to account for appropriate choices and monitoring of the products used. Decisions should always be evidence-based and in order to do this, records should be made both before and after use to quantify the effectiveness and to ensure that our decisions are objective and based on data rather than anecdote. Objective records should be maintained before and at the end of treatment in order that evaluations of efficacy can be made against the originally intended endpoints. Endpoints when using antibiotics must relate to the spectrum of the antimicrobial product and not just clinical signs. Antimicrobial resistance is an increasing problem in human and animal health (Reeve-Johnson, 2000c). As dispensers of the antimicrobials which select for the survival of resistance genes in the bacterial population, it should be viewed as an obligation to monitor both our patients and our clinic environments for resistant bacterial strains and to use antimicrobials at the appropriate dose and full treatment duration even when clinical signs have resolved.

In summary there are 10 practical actions which are attainable in the average clinical practice:

1. Decide the precise end point of treatment in advance for each case (for example, bacterial elimination)
2. Determine the site of activity that the antimicrobial needs to reach in order to achieve this (for example, ECF / organ / intracellular) and define your choice of antibiotic options based upon this.
3. Consider the toxicological profile and potential side effects for the chosen product and asses whether this restricts the dose.
4. Even if presumptive treatment is made, take a bacterial swab first!
5. Conduct an MIC test and with reference to the product data assess whether the concentration reaches the MIC at the site of activity and for how long. If it does not exceed the MIC and remains above this for at least 75% of the dose interval, the chances of successful elimination of infection are reduced.
6. Use the antibiotic at the recommended dose and for the full recommended duration.

Table 2: Example of a datasheet recording the use and outcome of antibiotics treatment in 2 patients

Pyoderma treatment log

Date	Patient identity	Bacterial culture	Desired endpoint	MIC i g/mL	Drug	Dose	Treatment duration	Final bacterial culture	Final MIC	Notes	Relapse date
5 May 05	Millie Harris	*Staphaureus*	Bacterial elimination & clinical resolution	2.0	Potentiated amoxycillin	15 mg/kg bid	28 days	Nil	NA	Bacterial elimination & clinical resolution	
6 May 05	Serg' Smith	*Staph aureus*	As above	4.0	Potentiated amoxycillin	15 mg/kg bid	5 days	*Staph aureus*	4.0	Owner wanted to discontinue treatment. Clinical signs much reduced, bacterial elimination not achieved – advise continue tratment	20 May 05
11 May 05	Serg' Smith	*Staph aureus*	As above	4.0	Potentiated amoxycillin	15 mg/kg bid	14 days	not done	not done	Clinical signs resolved, owner would not pay for bacterial swab	
20 May 05	Serg' Smith	*Staph aureus*	As above	4.0	Potentiated amoxycillin	15 mg/kg bid	14 days	*Staph aureus*	8.0	*Staph aureus* still present? Resistant? Elect to change antibiotic	
3 Jun 05	Serg' Smith	*Staph aureus*	As above	8.0	Enrofloxacin	2.5 mg/kg bid	21 days	Nil	NA	Bacterial elimination & clinical resolution	

7. Always re-examine cases at the end of treatment for clinical success and it may be worth taking a swab to check for bacterial elimination (this should be viewed as a responsibility of a dispenser, a duty to the patient and client and makes financial sense for the clinic!).
8. Pay particular attention to relapsed cases; *always* take a swab and culture for the organism from these cases (try to distinguish whether there is a partial cure with re--growth, antimicrobial ineffectiveness due to lack of spectrum or penetration or whether there are resistant strains needing alternative drugs to eliminate them. Be sure that your clinic is not an environmental reservoir of resistant organisms, especially multi drug-resistant *Staphylococcus aureus* strains).
9. Evaluate the patient in terms of the originally intended end point.
10. Record your findings!

An example of a simple data set which can be generated for each type of case could be seen in Table 2 :

CONCLUSION

The veterinary practitioner is highly empowered in influencing the extent to which different treatment options are utilised in the marketplace. Clearly this can have a profound effect on the size and value of the market to the drug developer. The responsibility for this 'gatekeeper role' of determining provision should be evidenced by the combination of a sound veterinary training in pharmacological concepts, and up to date knowledge of current therapeutics and a commitment to evidence-based medicine where diagnosis and prescription is made using evidence and follow up on all cases using prescription products. This protects against overuse and ensures that therapy is continued until the appropriate end point.

The theoretical efficacy of a drug can be modelled on the assumption that the effectiveness in the field is determined by the distribution, concentration and time the antimicrobial is available in the tissues. Many factors can limit the practical application of this as a predictive science, such as the susceptibility of the organism, the immuno-competence of the patient and non-pharmacologic factors such as the way animals are housed and managed and the infection pressure in their environment. In clinical practice the luxury of predictive pharmacology tailored to the individual is generally not available. Sensitivity testing is easily carried out for the commonly encountered veterinary pathogens. This can be utilised to monitor success in individual treatment cases as well as surveillance for accumulation of resistant organisms within the clinic environment. Using the appropriate dose and duration of antimicrobial is a key part of limiting the risk of increasing antimicrobial resistance in a market where the incentive to innovate by pharmaceutical companies only matches the growth in the overall size of the market, which is greatly influenced by practising clinicians.

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