# Using the Veterinary Antimicrobial Decision Support (VADS) System to Evaluate Therapeutic Regimens

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## Abstract

The goal of the Veterinary Antimicrobial Decision Support (VADS) System is to support the veterinary profession in preserving the efficacy of antimicrobials for therapeutic use in animals and humans. Enabling the practicing veterinarian to efficiently access and utilize currently available information when making antimicrobial use decisions is a critical component in the judicious use of antimicrobials in food animals. Emphasis is placed on approved drugs and regimens, with additional information provided when extralabel regimens are required for refractive pathogens, or where no effective approved therapy exists. Initial development is aimed at applications in cattle and swine, with poultry and small ruminant applications to follow. System inputs for antimicrobial regimen construction include pathogen susceptibility data, drug pharmacokinetics and pharmacodynamics, and clinical trial data. Regimen recommendations are developed by the collaborators and reviewed by veterinary clinical experts prior to being included in the system. The data and methods used to develop regimen recommendations are available for review on the web site. Information resources for ancillary/alternative therapies and disease epidemiology will also be available on the site. Clinical efficacy data is being evaluated to support label and extralabel uses of antimicrobials presented in the VADS System. The web site will contain a mechanism for users to contact the VADS System collaborators to give feedback on regimen efficacy, rationality of regimens, and errors or omissions in modeling. Transparency of data sources and modeling procedures will invite input to improve the system.

## Introduction

The goal of the Veterinary Antimicrobial Decision Support (VADS) System is to support the veterinary profession in preserving the efficacy of antimicrobials for therapeutic use in animals and humans. Enabling the practicing veterinarian to efficiently access and utilize currently available information when making antimicrobial use decisions is a critical component in the judicious use of antimicrobials in food animals.

The VADS System is being developed as a web-based, peer-reviewed system centered on therapeutic applications. The project collaborators are: Dr. Mike Apley, Iowa State University College of Veterinary Medicine; Dr. Virginia Fajt, Pueblo, CO; Dr. Cory Langston, Mississippi State University College of Veterinary Medicine; and Dr. Jeff Wilcke, Virginia-Maryland Regional College of Veterinary Medicine.

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There are 4 basic components to regimen development for extralabel uses in the VADS System.

1. How is the antimicrobial absorbed, distributed and excreted from the body of food animals (pharmacokinetics)?

2. How is the antimicrobial best presented to the target pathogen (pharmacodynamics)?

3. What is the amount of the antimicrobial required to inhibit growth or kill the pathogen (susceptibility testing)?

4. Do the results of regimen modeling hold true under clinical conditions?

The VADS System project began in 1999 with commitments for three years of support from The Academy of Veterinary Consultants, The American Association of Bovine Practitioners, The National Cattlemen's Beef Association, The American Veterinary Medical Associa-

tion and The American Association of Swine veterinarians. Additional start up support was provided by the National Pork Board and the Iowa Beef Center. Five years of support in the form of a collaborative agreement with the Food and Drug Administration Center for Veterinary Medicine began in April of 2001.

### Gathering Data from the Literature

An extensive initial search was performed to gather articles addressing pharmacokinetics of antimicrobials in food animals, pharmacodynamics of antimicrobials, susceptibility of animal pathogens and therapeutic trials. Since the time of this search, weekly current contents searches have been conducted within three editions.

- Agriculture, Biology, & Environmental Health Sciences
- Clinical Medicine
- Life Sciences

Within these editions, Current Contents searches were conducted through approximately 3,500 journals. Our search statement profiles consist of multiple key words (and various forms of these key words) as well as exclusion terms for some journals which have been low yield for pertinent articles. Table 1 gives the number of articles under review for the database as of February, 2002 and additions in the next year. The additions have been selected based on review of title and abstract prior to obtaining the article. Not all of these articles will be of sufficient quality or have appropriate data for inclusion in the VADS System.

Dr. Wilcke has constructed a reference matrix to allow the VADS System user to evaluate the literature sources used and rejected for use for specific therapeutic applications. A searchable database of article citations is currently available on the website. The system is designed to be completely transparent as to data used to construct regimens. The goal is for users to critically evaluate system input and inform the collaborators if there is an error in interpretation or an omission of pertinent data.

**Table 1.** Articles in the VADS System database by date.

| Keyword | February 2002 | February 2003 | Year additions |
|---|---|---|---|
| All VADS Articles | 2330 | 2559 | 229 |
| Pharmacokinetics | 750 | 809 | 59 |
| Susceptibility | 374 | 454 | 80 |
| Therapy | 837 | 927 | 90 |
| Pharmacodynamics | 75 | 91 | 16 |

### Pharmacokinetic Data Evaluation and Modeling

Standard operating procedures (SOPs) for evaluating pharmacokinetic literature, performing additional modeling of available data, and presenting extralabel antimicrobial regimens in relationship to MIC breakpoints have been developed. An example of the procedures used for developing extralabel regimens for procaine penicillin G in calves is as follows.

1. The pharmacodynamic characteristics of penicillin G were used to develop the modeling approach for regimen construction. In the case of the beta-lactams, time above MIC is most closely linked to clinical efficacy. The time component varies by pathogen, with a minimum of approximately 50% of the dose interval above the pathogen MIC typically targeted for Gram (+) bacteria and the entire dose interval above the MIC considered a target for Gram (-) bacteria. To provide a conservative estimate in the VADS System (the dose may be slightly higher than actually required), a modeling target of 100% of the dosing interval above the MIC of the pathogen for 75% of the animal population was selected. This target is represented by the "trough" serum concentration immediately prior to the next dose at steady state. Steady state is achieved when the amount administered with each dose equals the amount excreted since the last dose was given, with approximately 90%, 95% and 99% of steady state concentrations achieved after 3.3, 5 and 7 elimination half-times, respectively. This target will vary by drug group and possibly pathogen.

2. Procaine penicillin G pharmacokinetic datasets in cattle from the literature were utilized to estimate the trough concentrations that would be observed after dose accumulation at steady state. Individual animal, time point concentration data (or mean time point data with variance estimates) are preferred because these data may be entered into a superpositioning program that will produce a calculated trough concentration with a population variation estimate at steady state. Superpositioning is the process of adding serum concentrations from consecutive doses to predict the concentrations that would occur at steady state due to dose accumulation. The program used to facilitate data superpositioning was developed by Dr. Langston. Superpositioning in this manner alleviates concerns about modeling assumptions when calculated, compartmental model data is

utilized to estimate trough and variance parameters. Compartmental modeling parameters may be used for regimen construction, but superpositioning of time point data is preferred.

3. The superpositioning program output is then used as the basis for Monte Carlo simulation utilizing @Risk, a risk analysis software program (Palisade Corporation, Newfield, NY). This approach allows creation of a "virtual herd" of animals with varying trough concentrations based on the superpositioned mean trough concentration and variance estimate. The trough concentration at which 75% of the modeled population is equal to or above this concentration is selected to represent the MIC of the organism that would be satisfactorily addressed by the regimen that generated the original dataset.

4. Multiple datasets (if available) are used to construct estimates of population troughs originating from different dosing regimens.[1-3] These trough estimates are used to construct a single regression line to describe the best regimens to address minimal inhibitory concentrations tested for pathogens in the target species. Examples of trough estimates from different data sets compared to linear regression for Q12h and Q24h intramuscular dosing of procaine penicillin G in cattle are presented in Figure 1. These modeled trough concentrations are lower than the reported means in these references because the estimate now applies to 75% of the population of cattle. The VADS System collaborators are not under the illusion that this will allow exact matching of pathogens to regimens, but it is expected to provide reasonable doses and to rule out doses that would be unreasonably high or low.

5. These regimen-MIC relationships are then presented in a format where the veterinarian may evaluate them in the context of an MIC derived from a submitted isolate, or in the context of susceptibility summaries presented to help facilitate reasonable empiric therapy. Table 2 gives examples of penicillin G susceptibility summaries from the ISU Diagnostic Laboratory for 2001. Data in the VADS System currently includes extended dilution susceptibility data for 2000 – 2002. Data is being collected from other diagnostic laboratories as well as from literature sources. In the VADS System, MICs of pathogens are matched to regimens derived from the modeled relationships illustrated in Figure 1. The user will be able to evaluate the regimens by the percent of isolates from different sources that would be predicted to be adequately addressed. Serial dilution MICs for the user's specific isolate may also be evaluated in light of these relationships. Examples of regimen-MIC relationship reporting are available to the public on the VADS website at VADS.org.

6. Withdrawal times for extralabel regimens are constructed by the Food Animal Residue Avoidance Databank (FARAD) and will be available on the site through cooperation with FARAD.

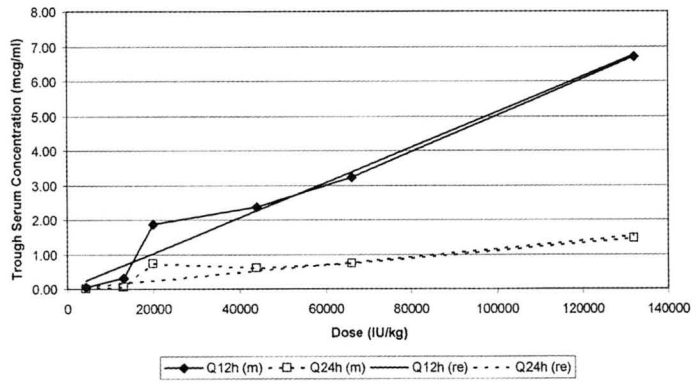


**Figure 1.** Modeled (m) and regressed (re) predicted trough serum concentrations for intramuscular procaine penicillin G (300,000 IU/ml) given every 12 hours (Q12h) or every 24 hours (Q24h) in cattle.

**Table 2.** Number of isolates by MIC (μg/ml) for 2001 bovine isolates from the Iowa State University Diagnostic Laboratory. Extended dilution testing ranged from 0.12 μg/ml to 8 μg/ml. Isolates not susceptible at 8 μg/ml are reported as ≥16 μg/ml. Data courtesy of Dr. Lorraine Hoffman and Tim Klinefelter.

| | N | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | ≥16 |
|---|---|---|---|---|---|---|---|---|---|
| *Haemophilus somnus* | 51 | 43 | 5 | | | 1 | 1 | | 1 |
| *Pasteurella multocida* | 138 | 100 | 21 | 2 | 5 | 1 | 4 | 2 | 3 |
| *Mannheimia haemolytica* | 130 | 55 | 40 | 6 | 1 | | | 4 | 24 |
| *Salmonella typhimurium* | 19 | | 1 | | | | | 3 | 15 |
| *Salmonella newport* (type C2) | 18 | | | | | | | | 18 |
| *Eschericia coli* K99 negative | 290 | | | | | 1 | | 3 | 286 |


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The data and procedures used in the construction of all extralabel regimens will be readily available for review and comment on the website.

## Clinical Confirmation

Clinical efficacy data is being evaluated to support label and extralabel uses of antimicrobials presented in the VADS System. There is a paucity of clinical data to support many extralabel uses in food animal medicine. It is the hope of the system collaborators that holes in pharmacokinetic and clinical data emphasized by system development will help to focus future research in food animal antimicrobial use.

## Feedback

The web site will contain a mechanism for users to contact the VADS System collaborators to give feedback on regimen efficacy, rationality of regimens and errors or omissions in modeling. Transparency of data sources and modeling procedures will invite input to improve the system.

## References


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