USP Veterinary Clinical Drug Information Monograph Development Process

The United States Pharmacopeia (USP) has developed clinical drug information monographs that provide evidence-ranked, species-specific extra-label recommendations, within a framework of compiled FDA-approved product label information, for the use of antibiotics in the major species, including cats and dogs. The development process was a collaborative effort between the USP Veterinary Medicine Information Expert Committees (VMI) that served from 1985 to the present and staff within the USP Veterinary Group. Committee members would decide which therapeutic categories, and drugs within each category, were of greatest need to the practitioner. For the antimicrobials, 22 monographs covering 63 selected medications were created.

Once drugs were selected by VMI for monograph development, a staff veterinarian obtained publicly available information on the drugs for review, including USA and Canadian label information, FDA Freedom of Information documents, foreign drug labels, and peer-reviewed journal articles. Careful attention was paid to species-specific information. This information was then arranged into a common template containing: brand names, category of drug, indications, regulatory considerations, chemistry, pharmacology and pharmacokinetics (i.e., mechanism of action/effect, absorption, distribution, protein binding, biotransformation, elimination), precautions to consider, side/adverse effects, overdose information, client consultation, veterinary dosing and dosage forms information.

Certain sections, such as chemistry and regulatory considerations, were not contentious. All reliable pharmacokinetic information found was added, regardless of species. The indication and dosing recommendations, however, required the greatest
effort, and VMI applied the most intensive evidence-based approach to reach a consensus on these two sections.

For each extra-label indication, and any label indication that was viewed as contentious by an Expert Committee member, a species-specific evidence table summarized all pertinent items of literature. The table would contain the citation information, the type of study [e.g., case report(s), clinical trial, disease model, \textit{in vitro} study, meta-analysis, pharmacokinetic study without surrogate endpoints, pharmacokinetic study with surrogate endpoints], method of randomization, type of control used (e.g., positive, negative, uncontrolled), and the type of masking used (e.g., single-masked, double-masked, nonmasked). A synopsis of the clinical methods used, doses and duration of therapy studied, results, author conclusions, and limitations noted by the USP staff veterinarian were included. A portion of an example evidence table is given in Figure 1.

When all of the evidence tables for a particular drug or family of drugs had been constructed, they were integrated into a monograph ballot provided to VMI Expert Committee members and third-party \textit{ad hoc} reviewers for initial discussion. Therefore, reviewers had access to the evidence tables and all other information compiled for that drug (including labeled indications, pharmacokinetic and safety data) during the decision-making process.

Once a preliminary consensus on the indications that would be included in the monograph was reached, a species-specific statement for each indication to be included was drafted and placed into one of three categories. “Accepted” indications were those that had substantial data supporting them and were in common use. The majority of these
were indications included in current product labeling, but extra-label indications also
were included if they rose to the required level of evidence. The “Potentially effective”
category (also known as “Acceptance not established” in the older USP information
monographs) included indications with moderate evidence to support a particular use,
often addressing an unmet clinical need. Lastly, an indication may have been deemed
“Unaccepted,” meaning the drug should not be used for a given purpose. This latter
categorization was most often applied to older drugs that newer treatments had rendered
obsolete due to improved safety and/or efficacy. In addition, beginning in 2005, all new
monographs and revisions of older monographs included evidence ratings for each
indication. Each rating was composed of one overall Evidence Quality indicator and one
or more Evidence Type indicators (see Examples 1 and 2). The monograph identified
into which of the three categories an indication fell, combined with the drug product’s
evidence ratings, providing an evidentiary basis to support an indicated use.

The evidence tables created for extra-label indications were also used as part of
the discussions for corresponding dosage recommendations. In a few cases, tables were
specifically created to address a dosage controversy. Both extra-label indications and
dosing were assigned a designation to differentiate them from labeled recommendations
in each monograph.

The initial ballot allowed comments on any portion of the monograph, in addition
to requesting decisions on indications and dosing. It was typically followed by at least
one ballot summarizing the initial responses to issues on which a consensus was not
reached. Draft monograph revision and Expert Committee review continued until a
consensus was reached on all previously contentious sections. The monograph was then
listed for public review on USP’s web site, during which time copies of draft text were made available to the manufacturers of the drug, the Center for Veterinary Medicine/U.S. Food and Drug Administration, and all other interested parties for review and comment. Following public review the monograph was finalized, became part of USP’s authorized text (not FDA-enforceable), and was published. Monographs underwent periodic updates, as needed. USP monographs were the only drug information source in veterinary medicine which underwent such extensive evidence-based evaluation coupled with expert panel review, a process by which the scientific credibility of the information was maintained.

In December of 2008, USP underwent a significant staff reduction with a concomitant reduction or elimination of certain information programs, due to the worldwide economic downturn. There is no longer a veterinarian on staff to work with the VMI Expert Committee to develop and update the monographs and evidence tables. Most of the more than 100 evidence tables created during development of this evidence-based information are not publicly available. In September 2009, the Veterinary Clinical Drug Information monographs were transferred to the American Academy of Veterinary Pharmacology and Therapeutics and can be accessed on the website at http://www.aavpt.org/USPmonographs.shtml. The future development of this drug information resource is being discussed within the AAVPT and the American College of Veterinary Clinical Pharmacology.
**Example 1. Evidence table**

**Cefazolin in the prevention of perioperative infections in dogs.**

Revision date: June 16, 2008


<table>
<thead>
<tr>
<th>Design:</th>
<th>Goal:</th>
<th>Limitations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Randomized, blinded, controlled clinical trial</td>
<td>To investigate whether perioperative antibiotic administration reduces the risk of developing postoperative infection after elective orthopedic surgery.</td>
<td>• None were noted.</td>
</tr>
<tr>
<td>N = 126 total cases enrolled</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Methods:**

- Dogs presented for elective orthopedic surgery. Exclusions included surgery requiring internal fixation devices, dental procedures also performed, antibiotic given within the previous 30 days, open fractures, multiple limb trauma, infection near the incision site, and severe gingivitis or otitis externa.
- Only the pharmacist who made up the treatments knew which medication was given to each subject. Just before the surgery incision was closed, a culture swab was taken from the incision site. Specific criteria were set to evaluate whether postoperative infection had occurred.
- The authors expected to need 201 cases to have sufficient data for evaluation.

**Dose and duration:**

- Medications were administered 30 minutes before the first incision and, if surgery lasted more than 90 minutes, a second dose was given. Dogs were monitored for 10 to 14 days after surgery.
  - Group 1 (48 dogs)—Intravenous cefazolin, 20 mg per kg of body weight (mg/kg)
  - Group 2 (43 dogs)—Intravenous penicillin G, 40,000 units per kg of body weight
  - Group 3 (35 dogs)—Intravenous saline

**Results:**

- The study was ended early, based on the data from the first 112 dogs; significantly more in the control group developed infections (15.6%) than dogs treated with either antibiotic (3.8%). No significant difference in infection rate was found between the two groups receiving antibiotics.
- Using the infection rates found (6.3% for cefazolin-treated, 2.3% for penicillin G-treated, 14.3% for no antibiotic), 5,000 Monte Carlo simulations were run. The results suggested dogs that received no antibiotic developed infection significantly more frequently than those given antibiotics. No statistically significant difference could be found between the two groups treated with antibiotics.

**Conclusions:**

- Cefazolin or penicillin G should be equally effective in preventing postoperative infection from elective orthopedic surgery.
Example 2. Evidence ratings and Indication Statement

**Evidence Quality**

A. Good evidence to support a recommendation for use  
B. Moderate evidence to support a recommendation for use  
C. Insufficient evidence to support a recommendation for use  
D. Moderate evidence to support a recommendation against use  
E. Good evidence to support a recommendation against use

**Evidence Type**

1. Species-specific evidence from at least one large randomized and controlled trial (RCT) or multiple small RCTs  
2. Species-specific evidence from a small RCT, disease models, large case studies, pharmacokinetic studies using surrogate endpoints, or evidence from well-designed trials in a different species that is considered appropriate for comparison.  
3. Dramatic results from either well-designed, species-specific trials without controls, controlled trials without randomization, or small case studies.  
4. Pharmacokinetic studies without surrogate endpoints or well-designed pharmacodynamic studies in healthy animals  
5. *In vitro* studies  
6. Opinions of respected authorities on the basis of clinical experience or reports of expert committees.

**Example of an indication statement in the monograph**

*Dogs*  
**Accepted**  
*Perioperative infections (prophylaxis)*  
Cefazolin is used in the prevention of infections associated with surgery, including bone surgery, and caused by susceptible organisms, when the risk of infection is high or potentially severely damaging (Evidence rating: A-1,2). {R-1;2;6;82;83}  

*EL US, CAN* indicates an extra-label indication in the U.S. and Canada.