Drug Piracy II: Quality, Efficacy and Safety Issues Related to Drug-Pirated Products ("compounded drugs") and the Claims Associated with Them

Joseph J. Bertone, *DVM, MS, Diplomate ACVIM*
Western University of Health Science, Pomona, CA 91766

Introduction

Veterinarians have enjoyed a remarkably positive reputation with the public. However, the use of pirated drugs has put that good reputation dangerously at risk. These drugs may be less expensive, but they also are of poor quality, highly variable in nature, and of unknowable content or stability. It follows, then, that use of pirated drugs removes the essential information in clinical pharmacology and application of therapeutics - i.e., what have you administered to the patient? With pirated drugs, neither you nor the pirate know what you have administered. Use of pirated drugs is, by definition, substandard veterinary care.

Definitions

See definitions in the article entitled "Drug Piracy I".

What is the Essential Information Necessary in Medical Therapeutics?

Answer: What and how much have you administered!

All clinical practice, clinical outcomes and pharmacologic data are based on that premise. If you don't know that information, then you are stabbing in the dark in applying a therapeutic. If you don't know what you have administered, then it is best "to apply the drug liberally *per foot*."

Question: How does a practitioner know what he or she has administered?

The best means is by administering an FDA approved drug. These include pioneer and generic drugs, and registered products. All these are manufactured under Good Manufacturing Practices (GMP) legislation and guidelines. GMP laws and guidelines provide assurance of the products' quality, consistency, strength, purity and stability.

Pioneer drugs are the original product under which drug sponsors collected efficacy and safety data for FDA approval (i.e., Rompun™). Generic drugs are allowed to be marketed based on matching pharmacokinetics to the pioneer (bioequivalence) and the determination that the other constituents of the product (excipients) provide no safety risk (e.g., Xylazine HCl Injection). As with pioneer products, generic products require FDA approval and undergo GMP manufacturing and assurance. Examples of registered products include intravenous fluids and vitamins, with no claim, but are allowed to be marketed by FDA and still undergo GMP manufacturing criteria.

A common misconception by veterinarians, and often indicated by drug pirates, is that pirated drugs are generics. That is wrong!

Pirated drugs can have no claim to quality, consistency, purity and stability. The bulk product is often made in laboratories in China, India, and Pakistan. These laboratories do not meet the requirements for GMP manufacturing as bulk-drug sources. No bulk drug intended for use in veterinary species is allowed to be imported into the US. Therefore, all bulk chemicals used in drug piracy have been imported illegally.

Excipients

Our education is unfortunately weak in pharmacology as it relates to drug formulation. A drug is far more than the active ingredient. In fact, the pharmacodynamics of a drug are heavily dependent on the exipients (i.e., inert substances and preservatives) that make up the formulation. Under GMP laws and guidelines, excipient quality is scrutinized to the same detail as the active ingredient.

Shelf-life

Accurate shelf-life studies for an FDA approved drug require GMP manufacturing so the drug can be assured of its composition. Once bottled, the drug undergoes accelerated testing for stability under extreme environmental situations before it is approved and given a shelf-life period. After that, aliquots of each batch are held back and tested over time. Cost for just the accel-

erated study for a single-dosage size will be approximately $150,000. Since pirated products are not GMP manufactured, even if one were to run accelerated studies, they would have no value because you could not be assured of the products, make-up and consistency from batch to batch. So, when pirates label their products with shelf-lives that exceed the period of the prescription (sometimes years) they are ignorant or unethical (see Figure 1).

How do the Illegal Pirated Drugs Compare?

Pirated drugs compare very poorly in that they are of poor quality, strength and purity.[2] See Figures 2 to 4. As an example, you intend to administer a drug X at a dose of 10 mg/kg. When you use an FDA approved drug, produced under GMPs (which is all of them) the dose you are administering will fall in the range of 9 to 10.5 mg/kg for most drug products. That is clinically reasonable.

Based on information collected to date when you use a pirated drug, and if you dose on volume for 10 mg/kg, the dose range you administer will be 0 to 17.6 mg/kg, with possible impurities and other "stuff" in the mix for which you can't account. Also there is no guarantee of purity and shelf life of the mixture. In Figures 1 to 4, the content of active ingredient was evaluated in samples from multiple drug pirates (disguised as compounding pharmacists). The approved formulation varies between 90 and 105% of the label indication. Tested

Figure 1. A product with an expiration date that was five years past the date the product was made. Although not a pirated product, this is clear evidence of the pirate's ignorance or unethical nature.

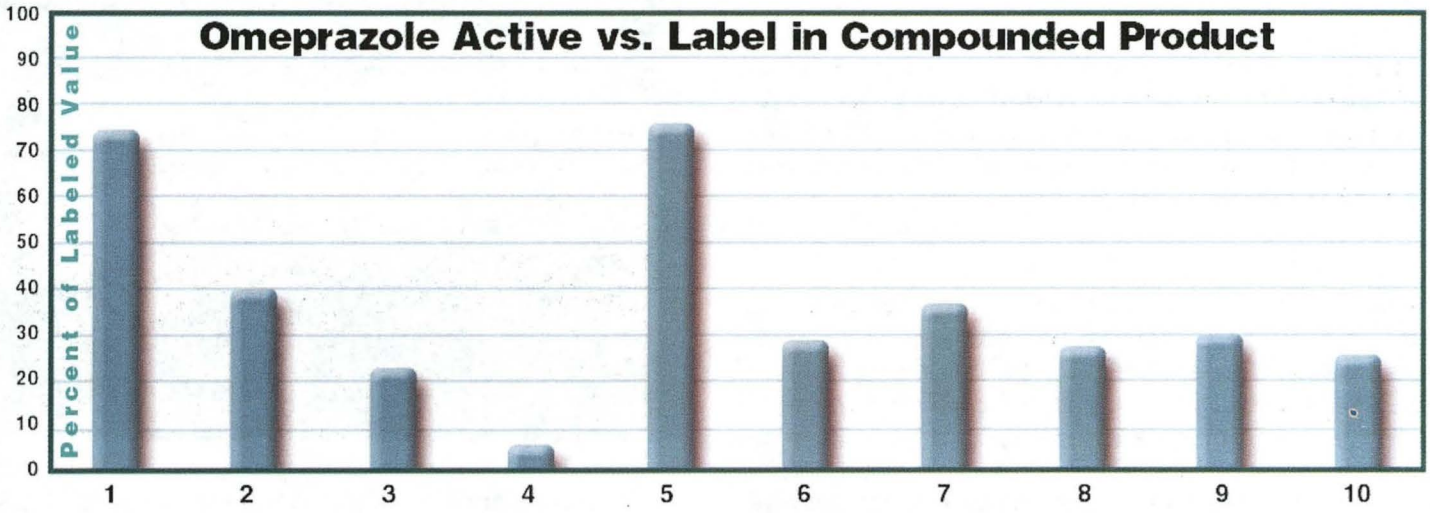

Figure 2. Omeprazole content as a percent of the label indication from 10 different drug pirates (Provided by Merial Animal Health, Inc).

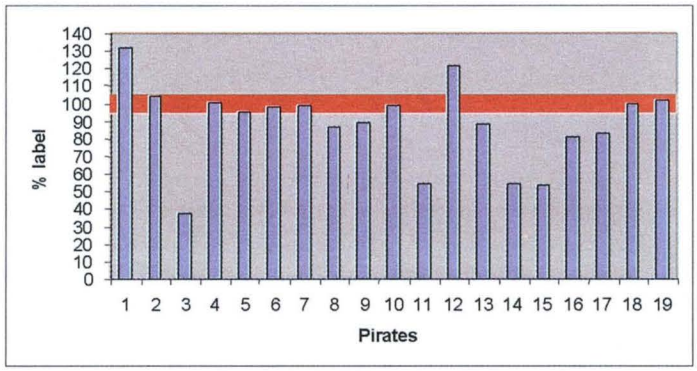

Figure 3. Meloxicam content as a percent of the label indication from 19 different drug pirates (Provided by Boehringer Ingelheim Vetmedica, Inc.). The orange region indicates tolerance of the product from an FDA approved source.

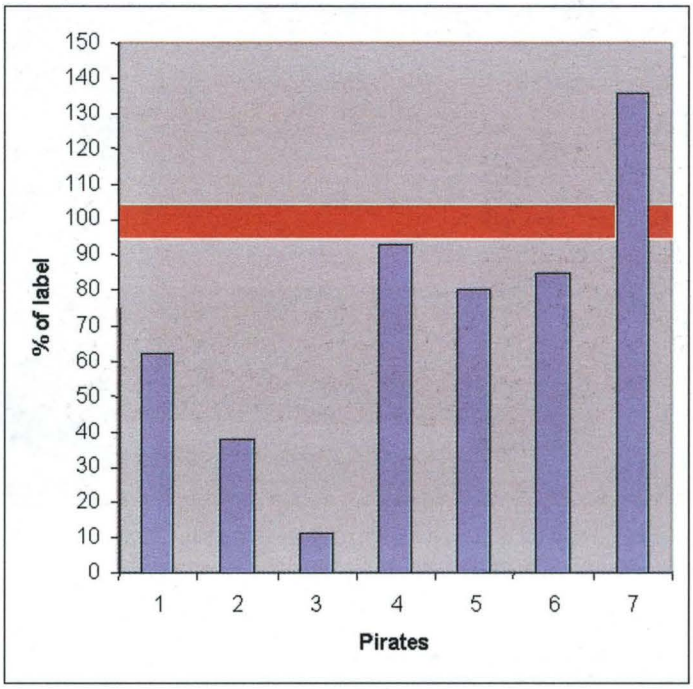

Figure 4. Clenbuterol content as a percent of the label indication from seven different drug pirates (Provided by Boehringer Ingelheim Vetmedica, Inc.). The orange region indicates tolerance of the product from an FDA approved source.

pirated articles to date have fallen in the range of 0 to 176% of the label indication. The variation is astounding. However, do not believe that these numbers are repeatable per pharmacy. Since the active ingredient from overseas sources is of variable quality, on the next round of batch testing, the high content pirated drug may look like the low content pirated drug and vice versa.

It makes sense that pirated drugs are poor quality. Pirates are unethical (they care little about you, your patients or your clients) or unknowledgeable (they believe they produce products to acceptable clinical standards).

Use of pirated products is not quality veterinary medicine.

How Does Drug Piracy Negatively Impact Quality Medicine?

That should now be obvious. When you use a pirated product, you are administering a poor, unacceptable quality drug, at an unknowable dose and questionable purity and sterility. In addition, this reduces incentive by the regulated pharmaceutical industry for scientific development of quality products for veterinary species. Several animal health sponsors have not moved forward with development of needed veterinary drugs because of the risk of having the product compounded. As an example, see Figure 3. That data was collected within a few weeks of the drugs FDA approval. At that point, the sponsor was a small player in marketing and distribution of the product. Why would a pharmaceutical company want to invest millions into something that pirates have to invest so little? Pirates violate the public trust with the veterinary professions' help.

How do you Choose a Good Compounding Pharmacy?

Let me make this clear: legitimate compounding pharmacy is not drug piracy. In fact, the American Col-

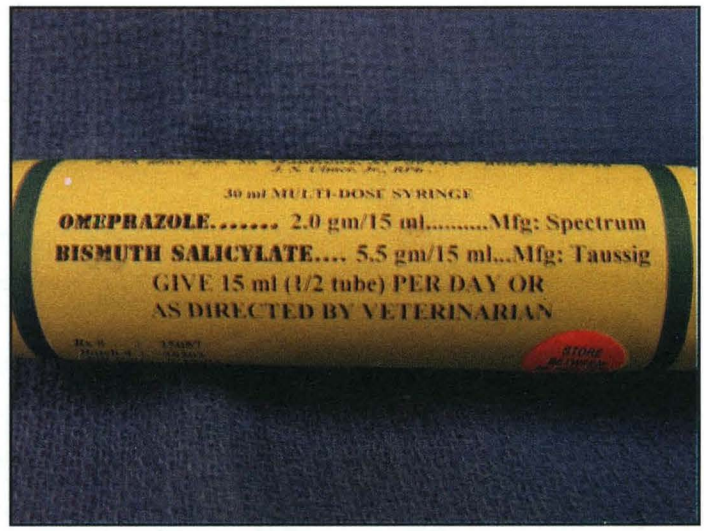

Figure 5. A combination of "omeprazole" and bismuth subsalicylate in a water based paste. Both BSS and water rapidly degrade omeprazole.

lege of Veterinary Pharmacists[1] indicated they are appalled by this activity and are being inadvertently and adversely affected by this practice. Legitimate pharmacy drug compounding is based on the extent of knowledge in compounding chemistry, and ethical behavior. They provide the best possible quality under the limited facilities and controls of a compounding pharmacy. It is very difficult to identify the extent of a pharmacist's knowledge in compounding and formulation chemistry. However, the pharmacist's ethical behavior can be evaluated. Good compounding pharmacists do not drug pirate.

Conclusion

You have no idea of the content of active ingredient or impurities in a pirated drug product. You also have no idea of the pharmacokinetics of the formulation. Drug piracy is an indication that the pirate is unethical or unknowledgeable. Hence, these drugs have no assurance of quality, safety and efficacy.

References

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